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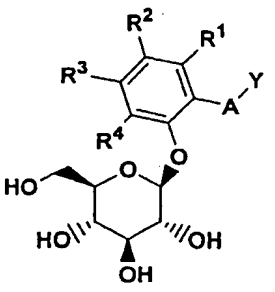
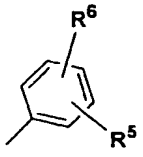
(54) Title: O-ARYL GLUCOSIDE SGLT2 INHIBITORS AND METHOD



(I)



(a)

(57) Abstract: Formula (I) wherein Y is formula (a) or heteroaryl; A is $-O(CH_2)_m$, S, $-NH(CH_2)_m$, or $(CH_2)_n$ where n is 0-3 and m is 0-2; and R^1 to R^6 are as defined herein. A method is also provided for treating diabetes and related diseases employing an SGLT2 inhibiting amount of the above compound alone or in combination with one, two or more other antidiabetic agents, and/or one, two or more hypolipidemic agents.

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O-ARYL GLUCOSIDE SGLT2 INHIBITORS AND METHOD

The present invention relates to O-aryl glucosides which are inhibitors of sodium dependent glucose transporters found in the intestine and kidney (SGLT2) and to a method for treating diabetes, especially type II diabetes, as well as hyperglycemia, hyperinsulinemia, obesity, hypertriglyceridemia, Syndrome X, diabetic complications, atherosclerosis and related diseases, employing such O-aryl glucosides alone or in combination with one, two or more other type antidiabetic agents and/or other type theraeutic agents such as hypolipidemic agents.

Approximately 100 million people worldwide suffer from type II diabetes (NIDDM), which is characterized by hyperglycemia due to excessive hepatic glucose production and peripheral insulin resistance, the root causes for which are as yet unknown. Hyperglycemia is considered to be the major risk factor for the development of diabetic complications, and is likely to contribute directly to the impairment of insulin secretion seen in advanced NIDDM. Normalization of plasma glucose in NIDDM patients would be predicted to improve insulin action, and to offset the development of diabetic complications. An inhibitor of the sodium-dependent glucose transporter SGLT2 in the kidney would be expected to aid in the normalization of plasma glucose levels, and perhaps body weight, by enhancing glucose excretion.

The development of novel, safe, and orally active antidiabetic agents is also desired in order to complement existing therapies, including the sulfonylureas, thiazolidinediones, metformin, and insulin, and to avoid the potential side effects associated with the use of these other agents.

Hyperglycemia is a hallmark of type II diabetes (NIDDM); consistent control of plasma glucose levels in diabetes can offset the development of diabetic complications and beta cell failure seen in advanced disease. Plasma glucose is normally filtered in the kidney in the glomerulus and actively reabsorbed in the proximal tubule. SGLT2 appears to be the major transporter responsible for the reuptake of glucose at this site. The SGLT specific inhibitor phlorizin or closely related analogs inhibit this reuptake process in diabetic rodents and dogs resulting in normalization of plasma glucose levels by promoting glucose excretion without hypoglycemic side effects. Long term (6 month) treatment of Zucker diabetic rats with an SGLT2 inhibitor has been reported to improve insulin response to glycemia, improve insulin sensitivity, and delay the onset of nephropathy and neuropathy in these animals, with no detectable pathology in the kidney and no electrolyte imbalance in plasma. Selective inhibition of SGLT2 in diabetic patients would be expected to normalize plasma glucose by enhancing the excretion of glucose in the urine, thereby improving insulin sensitivity, and delaying the development of diabetic complications.

Ninety percent of glucose reuptake in the kidney occurs in the epithelial cells of the early S1 segment of the renal cortical proximal tubule, and SGLT2 is likely to be the major transporter responsible for this reuptake. SGLT2 is a 672 amino acid protein containing 14 membrane-spanning segments that is predominantly expressed in the early S1 segment of the renal proximal tubules. The substrate specificity, sodium dependence, and localization of SGLT2 are consistent with the properties of the high capacity, low affinity, sodium-dependent glucose transporter previously characterized in

human cortical kidney proximal tubules. In addition, hybrid depletion studies implicate SGLT2 as the predominant Na^+/glucose cotransporter in the S1 segment of the proximal tubule, since virtually all Na-dependent glucose transport activity encoded in mRNA from rat kidney cortex is inhibited by an antisense oligonucleotide specific to rat SGLT2. SGLT2 is a candidate gene for some forms of familial glucosuria, a genetic abnormality in which renal glucose reabsorption is impaired to varying degrees. None of these syndromes investigated to date map to the SGLT2 locus on chromosome 16. However, the studies of highly homologous rodent SGLTs strongly implicate SGLT2 as the major renal sodium-dependent transporter of glucose and suggest that the glucosuria locus that has been mapped encodes an SGLT2 regulator. Inhibition of SGLT2 would be predicted to reduce plasma glucose levels via enhanced glucose excretion in diabetic patients.

SGLT1, another Na-dependent glucose cotransporter that is 60% identical to SGLT2 at the amino acid level, is expressed in the small intestine and in the more distal S3 segment of the renal proximal tubule. Despite their sequence similarities, human SGLT1 and SGLT2 are biochemically distinguishable. For SGLT1, the molar ratio of Na^+ to glucose transported is 2:1, whereas for SGLT2, the ratio is 1:1. The K_m for Na^+ is 32 and 250-300 mM for SGLT1 and SGLT2, respectively. K_m values for uptake of glucose and the nonmetabolizable glucose analog α-methyl-D-glucopyranoside (AMG) are similar for SGLT1 and SGLT2, i.e. 0.8 and 1.6 mM (glucose) and 0.4 and 1.6 mM (AMG) for SGLT1 and SGLT2 transporters, respectively. However, the two transporters do vary in their substrate specificities for sugars such as galactose, which is a substrate for SGLT1 only.

Administration of phlorizin, a specific inhibitor of SGLT activity, provided proof of concept *in vivo* by

promoting glucose excretion, lowering fasting and fed plasma glucose, and promoting glucose utilization without hypoglycemic side effects in several diabetic rodent models and in one canine diabetes model. No adverse effects on plasma ion balance, renal function or renal morphology have been observed as a consequence of phlorizin treatment for as long as two weeks. In addition, no hypoglycemic or other adverse effects have been observed when phlorizin is administered to normal animals, despite the presence of glycosuria. Administration of an inhibitor of renal SGLTs for a 6-month period (Tanabe Seiyaku) was reported to improve fasting and fed plasma glucose, improve insulin secretion and utilization in obese NIDDM rat models, and offset the development of nephropathy and neuropathy in the absence of hypoglycemic or renal side effects.

Phlorizin itself is unattractive as an oral drug since it is a nonspecific SGLT1/SGLT2 inhibitor that is hydrolyzed in the gut to its aglycone phloretin, which is a potent inhibitor of facilitated glucose transport. Concurrent inhibition of facilitative glucose transporters (GLUTs) is undesirable since such inhibitors would be predicted to exacerbate peripheral insulin resistance as well as promote hypoglycemia in the CNS. Inhibition of SGLT1 could also have serious adverse consequences as is illustrated by the hereditary syndrome glucose/galactose malabsorption (GGM), in which mutations in the SGLT1 cotransporter result in impaired glucose uptake in the intestine, and life-threatening diarrhea and dehydration. The biochemical differences between SGLT2 and SGLT1, as well as the degree of sequence divergence between them, allow for identification of selective SGLT2 inhibitors.

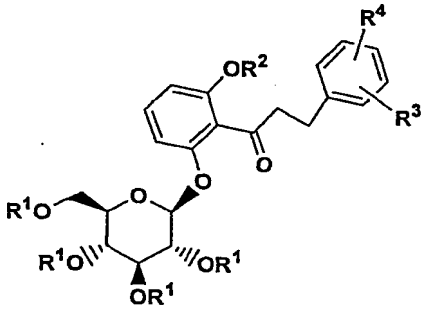
The familial glycosuria syndromes are conditions in which intestinal glucose transport, and renal transport of other ions and amino acids, are normal. Familial glycosuria patients appear to develop normally,

have normal plasma glucose levels, and appear to suffer no major health deficits as a consequence of their disorder, despite sometimes quite high (110-114 g/daily) levels of glucose excreted. The major symptoms evident in these patients include polyphagia, polyuria and polydipsia, and the kidneys appear to be normal in structure and function. Thus, from the evidence available thus far, defects in renal reuptake of glucose appear to have minimal long term negative consequences in otherwise normal individuals.

The following references disclose O-aryl glucosides SGLT2 inhibitors for treating diabetes.

EP 598359A1 (also JP 035988) (Tanabe Seiyaku) discloses compounds of the following structure **A**

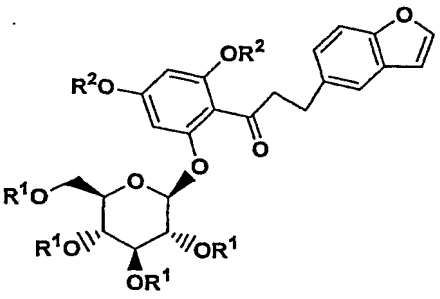
A



R^1 = H, acyl,
R^2 = H, Me
R^4, R^4 can be a variety of substituents

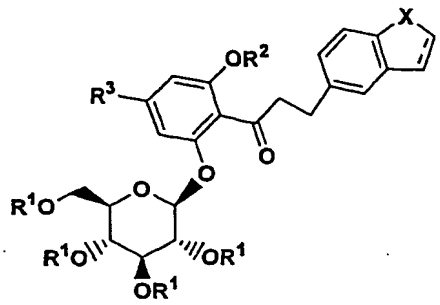
EP 0850948A1 discloses structures of the following genus **B**

B



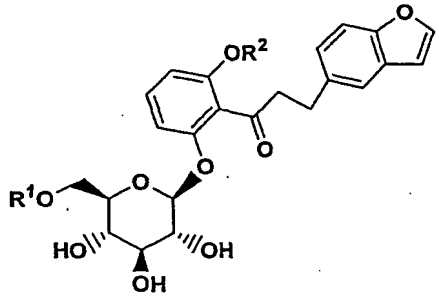
R^1 = H, acyl, CO(OAlkyl)
R^2 = H, allyl
R^3 = H or Me

JP 09188625A expands upon structure **B** to include examples of **B** where R^3 is H and where the 5 membered ring is saturated as well as the counterparts of benzothiophenes (O = S) and indenes (O = CH_2)



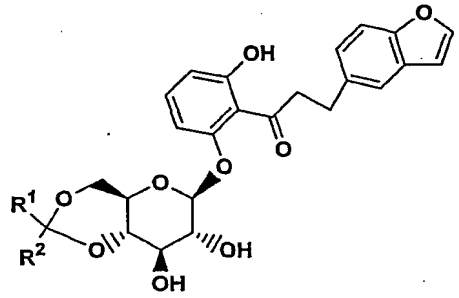
R^1 = H, acyl, CO(OAlkyl)
R^2 = H, allyl
R^3 = H or Me

JP 09124685A expands upon structure **B** for R^3 = H to include derivatives of mono acylated C6 hydroxyl where the acyl group is a substituted benzoic or pyridyl carboxylic acid or a urethane generated from the corresponding phenol.



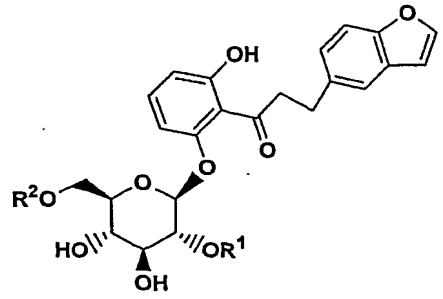
R^1 = H, acylaryll, CO(OAryl)
R^2 = H

JP 09124684 discloses derivatives of structure **B**



R^1, R^2 = H, alkyl, alkoxy, aryl or together oxo)

EP 773226-A1 discloses derivatives of structure **B**



R^1 = alkanoyl if R^2 = H
R^2 = alkoxycarbonyl if R^1 =H

JP 08027006-A discloses derivatives of structure **A** where various combinations of the glucose hydroxyl are acylated and appears to be similar to EP 598359A1

EP 684254-A1 appears to encompass derivatives of structure **B** disclosed in JP 09188625A.

Other disclosures and publications which disclose SGLT2 inhibitors are as following:

K. Tsujihara, et. al., Chem. *Pharm. Bull.* **44**, 1174-1180 (1996)

M. Hongu et. al., Chem. *Pharm. Bull.* **46**, 22-33 (1998)

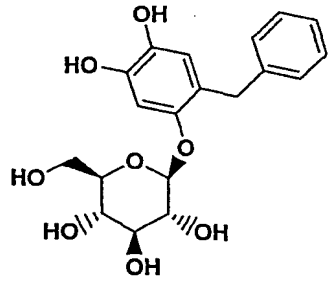
M. Hongu et. al., Chem. *Pharm. Bull.* **46**, 1545-1555 (1998)

A. Oku et. al., *Diabetes*,**48**, 1794-1800 (1999)

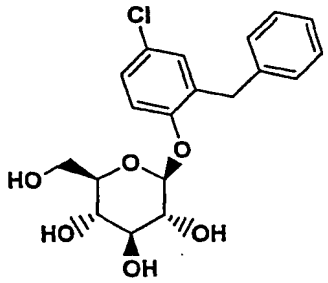
JP 10245391 (Dainippon) discloses 500 structures as hypoglycemic agents for treatment of diabetes. These are O-glucosides of hydroxylated coumarins.

Other references disclosing structures of O-arylglucosides, shown below, which are closely related to the genus disclosed herein are:

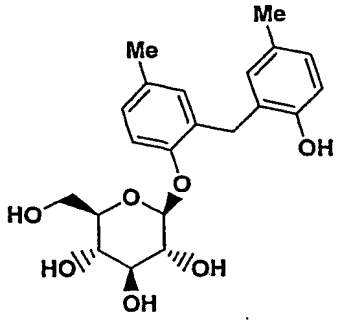
1) G. K. Jain et. al., Indian J. Chem., **26B**, 163-166 (1989)



2) A. Levai et. al., Acta Chim. Acad. Sci. Hung., **84**, 99-107 (1975)

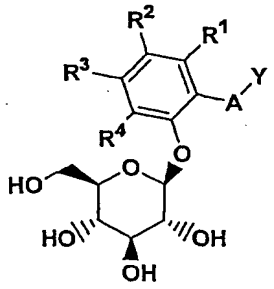


3) H. Kaemmerer et al., Makromol. Chem., **182**, 1351-1361 (1981)

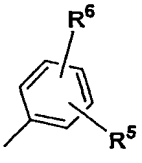


Description of the Invention

In accordance with the present invention, O-aryl glucoside compounds are provided which have the structure I.



wherein

when Y is  or heteroaryl;

R^1, R^2, R^3, and R^4 are the same or different and are independently selected from hydrogen, OH, OR^7, lower alkyl, or halogen, or two of R^1, R^2, R^3, and R^4 together with the carbons to which they are attached can form an annelated five, six or seven membered carbocycle or

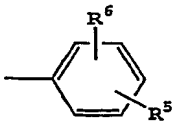
heterocycle which may contain 1 to 4 heteroatoms in the ring which are N, O, S, SO, and/or SO_2;

R^5 and R^6 are the same or different and are independently selected from hydrogen, OH, OR^{7a}, -OAryl, $-OCH_2Aryl$, lower alkyl, cycloalkyl, Aryl, arylalkyl, CF_3, arylalkenyl, $-OCHF_2$, $-OCF_3$, halogen, -CN, $-CO_2R^{7b}$, $-CO_2H$, COR^{8f}, $CHOHR^{8g}$, $CH(OR^{7h})R^{8h}$, $-CONR^8R^{8a}$, $-NHCOR^{7c}$, $-NHSO_2R^{7d}$, $-NHSO_2Aryl$, $-SR^{7e}$, $-SOR^{7f}$, $-SO_2R^{7g}$, $-SO_2Aryl$, $-OCH_2CO_2R^{7i}$, $-OCH_2CO_2H$, $-OCH_2CONR^{8b}R^{8c}$, $-OCH_2CH_2NR^{8d}R^{8e}$, or a five, six or seven membered heterocycle which may contain 1 to 4 heteroatoms in the ring which are N, O, S, SO, and/or SO_2, or R^5 and R^6 together with the carbons to which they are attached form an annelated five, six or seven membered carbocycle or heterocycle which may contain 1 to 4 heteroatoms in the ring which are N, O, S, SO, and/or SO_2;

R^7, R^{7a}, R^{7b}, R^{7c}, R^{7d}, R^{7e}, R^{7f}, R^{7g}, R^{7h}, and R^{7i} are independently lower alkyl;

R^8, R^{8a}, R^{8b}, R^{8c}, R^{8d}, R^{8e}, R^{8f}, R^{8g}, and R^{8h} are the same or different and are independently selected from hydrogen, alkyl,aryl, arylalkyl, cycloalkyl, or together with the nitrogen to which they are attached form an annelated five, six or seven membered heterocycle which may contain 1 to 4 heteroatoms in the ring which are N, O, S, SO, and/or SO_2;

A is $O(CH_2)_m$, S, $NH(CH_2)_m$, or $(CH_2)_n$ where n is 0-3 and m is 0-2, and a pharmaceutically acceptable salt thereof, all stereoisomers thereof, and all prodrug esters thereof.

The compounds of formula I of the invention as defined above also include the following provisos that where A is CH_2 and Y is 

and when

1) R^1 is OH and R^3 is alkyl, at least one of R^1, R^4, R^5 and R^6 is not hydrogen, and preferably 4-R^6 is other than hydrogen;
2) R^2 and R^3 are OH, at least one of R^1, R^4, R^5 and R^6 is not hydrogen, and preferably 4-R^6 is other than hydrogen;
3) R^2 is methyl, R^5 is OH, and R^6 is alkyl, at least one of R^1, R^3, and R^4 is not hydrogen; and
4) R^2 is chlorine, at least one of R^1, R^3, R^4, R^5 and R^6 is not hydrogen, and preferably 4-R^6 is other than hydrogen.

In the compounds of formula I, where A is $O(CH_2)_m$ or $NH(CH_2)_m$, the heteroatom O or N will be linked to the aryl ring directly joined to the glucoside moiety.

The compounds of formula I of the invention possess activity as inhibitors of the sodium dependent glucose transporters found in the intestine and kidney of mammals and are useful in the treatment of diabetes and the micro- and macro-vascular complications of diabetes such as retinopathy, neuropathy, nephropathy, and wound healing.

The present invention provides for compounds of formula I, pharmaceutical compositions employing such compounds and for methods of using such compounds.

In addition, in accordance with the present invention, a method is provided for treating diabetes, especially type II diabetes and related diseases including complications of diabetes, including retinopathy, neuropathy, nephropathy and wound healing, and related diseases such as insulin resistance, hyperglycemia, hyperinsulinemia, Syndrome X, elevated blood levels of fatty acids or glycerol, obesity, hypertriglyceridemia, atherosclerosis and hypertension, and for increasing high density lipoprotein levels, wherein a therapeutically effective amount of a compound

of structure I of the invention is administered to a human patient in need of treatment.

In addition, in accordance with the present invention, a method is provided for treating diabetes and related diseases as defined above and hereinafter, wherein a therapeutically effective amount of a combination of a compound of structure I of the invention and one, two or more of other types antidiabetic agents and/or one, two or more other types of therapeutic agents is administered to a human patient in need of treatment.

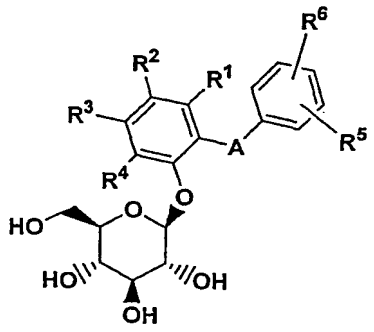
The conditions, diseases, and maladies collectively referred to as "Syndrome X" (also known as Metabolic Syndrome) are detailed in Johannsson *J. Clin. Endocrinol. Metab.*, 82, 727-34 (1997).

The term "other type of therapeutic agents" as employed herein refers to one or more antidiabetic agents (other than SGLT2 inhibitors of formula I), one or more anti-obesity agents, and/or one or more lipid-lowering agents (including anti-atherosclerosis agents).

In the above method of the invention, the compound of structure I will be employed in a weight ratio to the antidiabetic agent(s) and/or hypolipidemic agent(s) (depending upon its mode of operation) within the range from about 0.01:1 to about 300:1, preferably from about 0.1:1 to about 100:1, and more preferably from about 0.1:1 to about 10:1.

Preferred are compounds of formula IA

IA



wherein A is CH_2 or O or S.

More preferred are compounds of formula IA where A is CH_2;

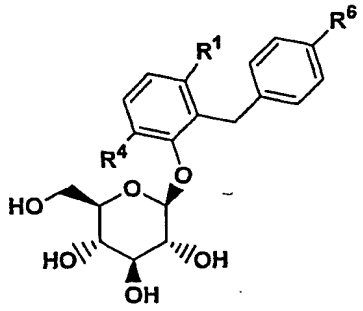
R^1 is H, halogen or alkyl;

R^2 and R^3 are each H;

R^5 is H.

Most preferred are compounds of formula I of the structure IB

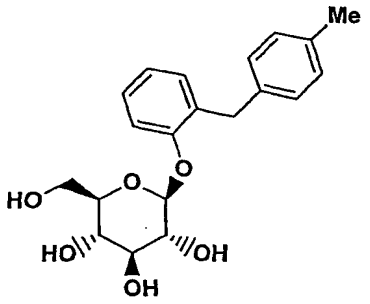
IB



where R^1 is hydrogen, halogen or alkyl or R^1 and R^4 are independently H or alkyl;

R^6 is hydrogen, alkyl, $R^{7a}O$, CHF_2O, CF_3O or $R^{7e}S$.

Examples of preferred compounds of formula I of the invention include compounds having the structure



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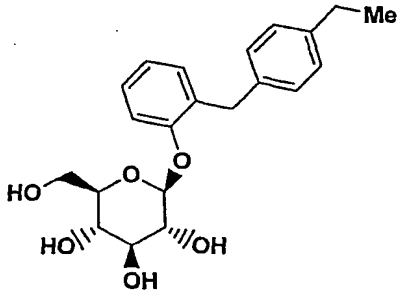

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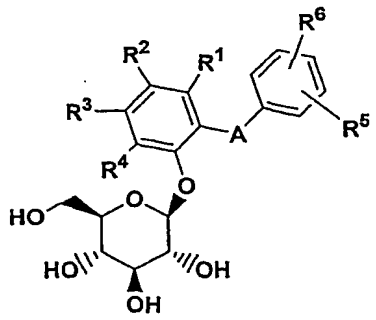


*R^6 = H unless otherwise indicated

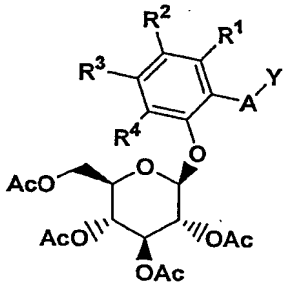
A	R^1	R^2	R^3	R^4	R^5
CH_2	H	H	H	H	4-MeO
CH_2	H	H	H	H	4-*t*Bu
CH_2	H	H	H	H	4-MeS
CH_2	H	H	H	H	4-*i*Pr
CH_2	H	H	H	H	4-Cl
CH_2	H	H	H	H	4-CF_3
CH_2	H	H	H	H	4-CF_3O
CH_2	Me	H	H	H	H
CH_2	H	H	H	Me	4-MeS
CH_2	H	H	H	Me	4-Me
CH_2	Cl	H	H	H	H

The present invention provides for compounds of formula I, pharmaceutical compositions employing such compounds and for methods of using such compounds.

The compounds of formula I of the invention may be prepared as shown in the following reaction schemes and description thereof wherein temperatures are expressed in degrees Centigrade.

Compounds of formula I of the invention can be prepared from compounds of formula II

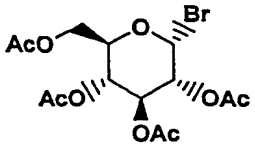
II



by treatment of II with a base such as LiOH or NaOH in a solvent such as 3:1 MeOH/H_2O or 3:2:1 MeOH/THF/H_2O.

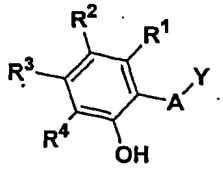
Compounds of formula II can be prepared by reacting commercially available 2,3,4,6-tetra -O-acetyl-α-D-glucopyranosyl bromide III

III



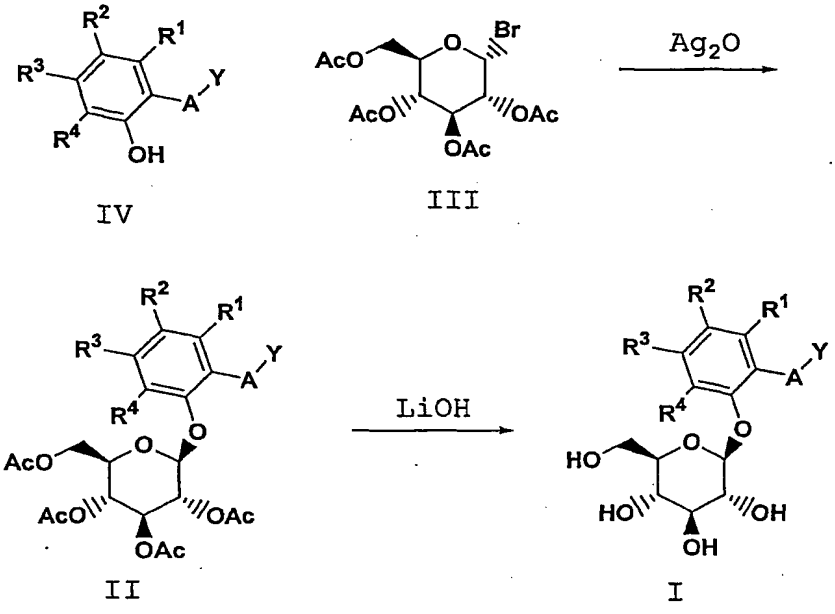
with compounds of formula IV

IV



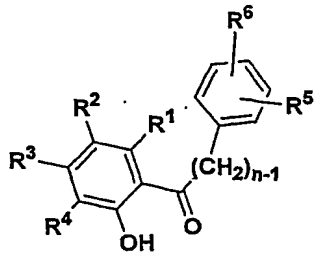
in the presence of Ag_2O in a solvent such as lutidine or quinoline or in the presence of silver triflate in a solvent such as CH_2Cl_2 containing a base such as 2,6-di-*t*-butyl-4-methylpyridine.

Scheme 1



Compounds of formula IV where A is $(CH_2)_n$ with n = 1-3 can be prepared from compounds of formula V

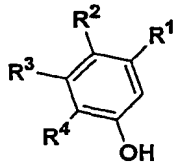
V



by treatment with H_2 in a solvent such as MeOH or EtOH in the presence of a catalyst such as Pd/C.

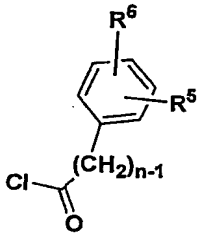
Compounds of formula V are either commercially available or readily prepared by acylation of compounds of formula VI.

VI



with compounds of formula VII

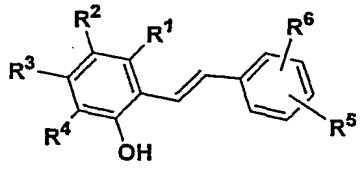
VII



by a variety of methods familiar to those skilled in the arts.

Compounds of formula IV where A is $(CH_2)_2$ can be prepared from commercially available compounds of formula VIII

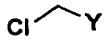
VIII



by treatment of VIII with H_2 in a solvent such as MeOH or EtOH in the presence of a catalyst such as Pd/C.

Compounds of formula IV where A is CH_2 can be prepared by alkylation of compounds formula VI with commercially available compounds of formula IX

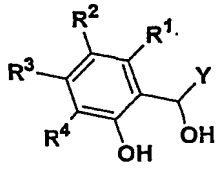
IX



using a solvent such as toluene and a base such as NaH provided that the aryl or heteroaryl ring of IX is not electron deficient i.e. the total Hammet σ for the substituents R^5 and R^6 is less than ~+0.3.

Compounds of formula IV where A is CH_2 can also be prepared from compounds of formula X

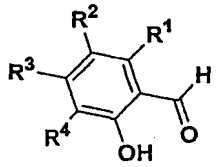
X



by reduction of X by with H_2 in a solvent such as MeOH or EtOH in the presence of a catalyst such as Pd/C or with a silane such as Et_3SiH in a solvent such as MeCN containing a Lewis acid such as TFA or $BF_3 \cdot Et_2O$.

Compounds of formula X are readily obtained by the reaction of commercially available compounds of formula XI

XI



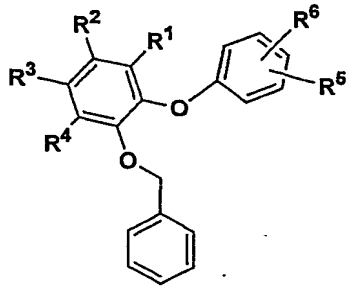
with the Mg^{+2} or Li^+ organometalic prepared from aryl or heteroaryl bromides or chlorides of formula XII

XII

using the procedures available to those skilled in the art.

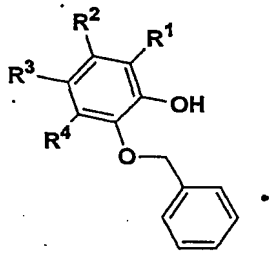
As seen in Scheme 2, compounds of formula IV where A is O can also be prepared by treating compounds of formula XIII

XIII



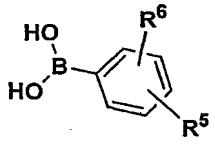
with H_2 in a solvent such as MeOH or EtOH using a catalyst such as Pd/C. Compounds of formula XIII can be prepared by reacting compounds of formula XIV

XIV



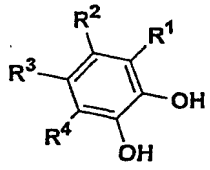
in a solvent such as pyridine containing Et_3N, molecular sieves, and $Cu(OAc)_2$ with compounds of formula XV

XV



Compounds of formula XIV are either commercially available or can prepared from the corresponding catechol XVI

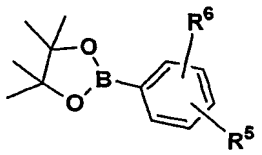
XVI



upon alkylation of XVI with one equivalent of benzyl bromide or chloride using procedures well known to those skilled in the art.

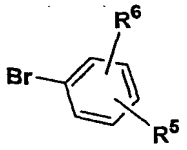
Compounds of formula XV are commercially available or can be obtained upon treatment of XVII with BCl_3 at -75° in a solvent such as CH_2Cl_2.

XVII



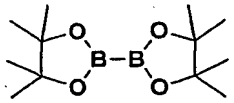
Compounds of formula XVII can be prepared upon heating compounds of formula XII

XII

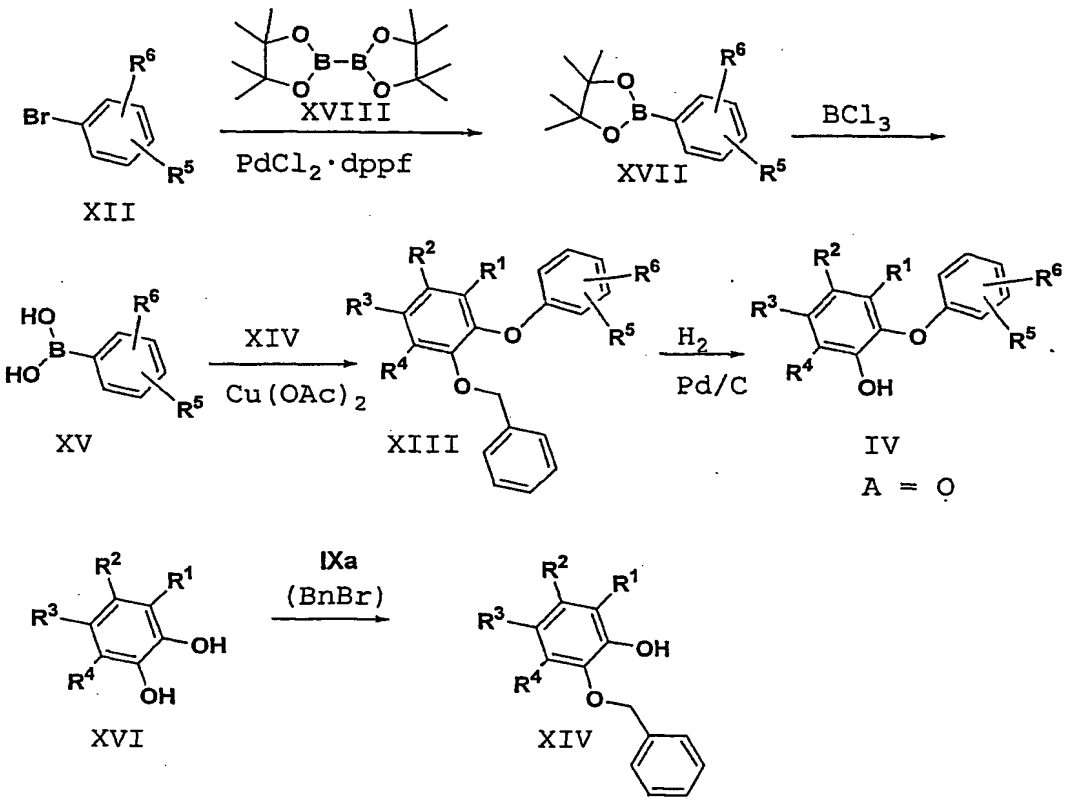


in a solvent such as DMSO containing a catalyst such as $PdCl_2 \cdot dppf$ and a base such as KOAc with compound XVIII.

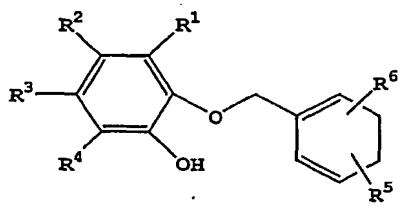
XVIII



Scheme 2

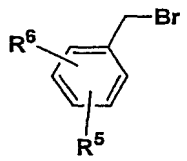


Compounds of formula IV where A is OCH_2 that is



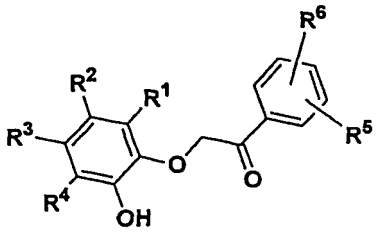
can be prepared by reacting compounds of XVI with benzyl halides of formula IXa in a polar solvent such as DMF or acetone containing a base such as Na_2CO_3 and a catalysis such as NaI.

IXa



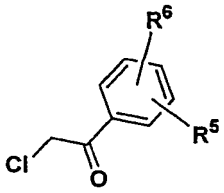
Compounds of formula IV where A is $O(CH_2)_2$ can be prepared by reacting compounds of XIX

XIX



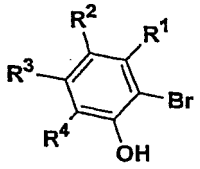
with H_2 in a solvent such as MeOH or EtOH using a catalyst such as Pd/C. Compounds of formula XIX are commercially available or may be prepared by alkylation of the compounds of formula XVI in a solvent such as acetone containing a base such as K_2CO_3 with commercially available phenacyl chloride or bromide of formula XX.

XX



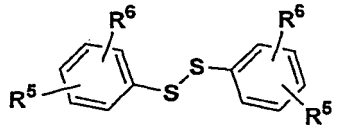
Compounds of formula IV where A is S can be prepared by treating compounds of formula XXI

XXI



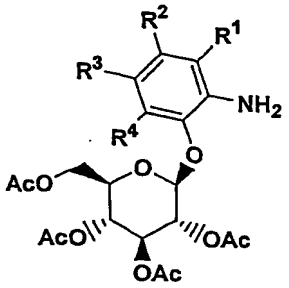
with 2 equivalents of t-BuLi at -78° in a solvent such as THF prior to the addition of compounds of formula XXII

XXII



As seen in Scheme 3, compounds of formula II where A is NH can be prepared by treating compounds of formula XXIII

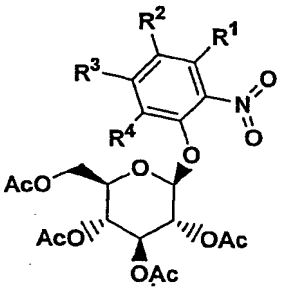
XXIII



with compounds of formula XV in a solvent such as Et_3N containing $Cu(OAc)_2$ and molecular sieves.

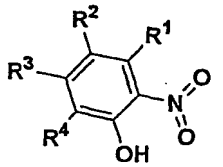
Compounds of formula XXIII can be prepared by treatment of compounds of formula XXIV

XXIV



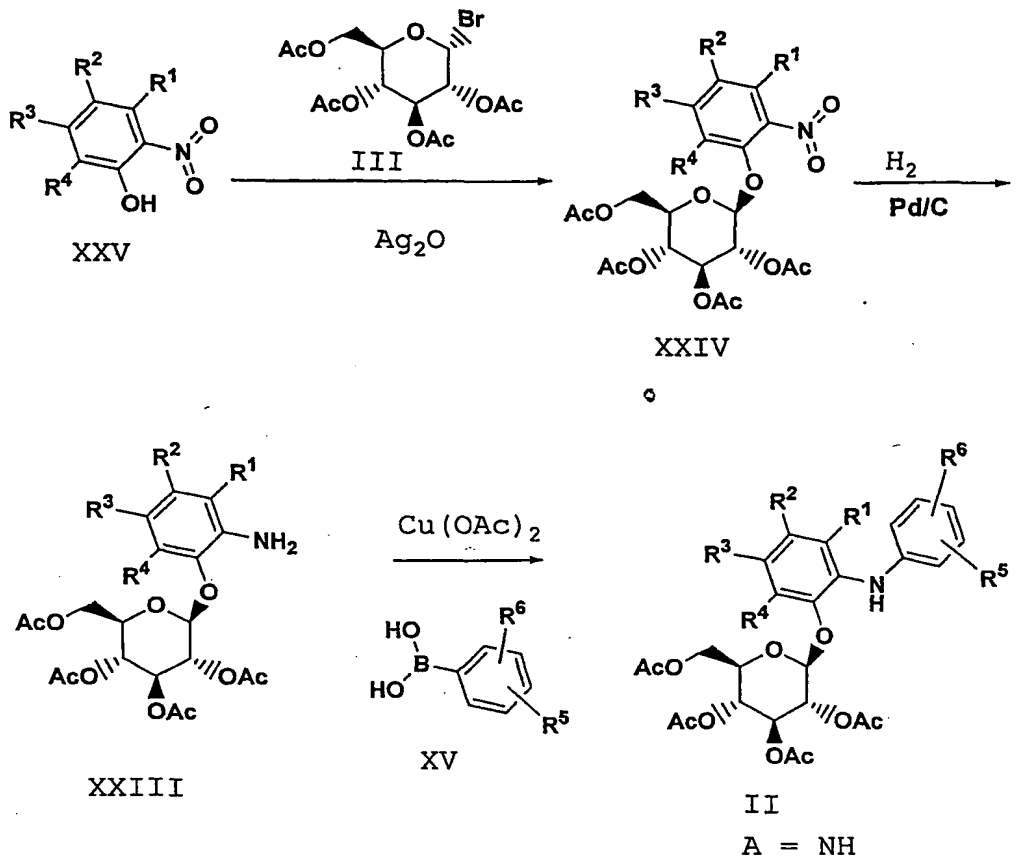
with H_2 using a catalyst such as Pd/C in a solvent such as MeOH or EtOH.

Compounds of formula XXIV can be prepared by coupling compounds of formula III with compounds of formula XXV



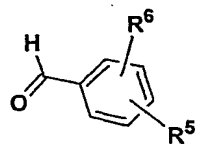
in a solvent such as lutidine or quinoline containing Ag_2O.

Scheme 3



Compounds of formula II where A is $NHCH_2$ can be prepared by coupling compounds of formula XXIII with compounds of formula XXVI

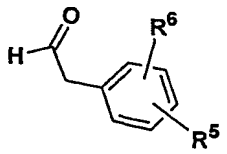
XXVI



by stirring in a solvent such as HOAc with a reducing agent such as $NaCNBH_3$.

Compounds of formula II where A is $NHCH_2CH_2$ can be prepared by coupling compounds of formula XXIII with compounds of formula XXVII

XXVII



by stirring in a solvent such as HOAc with a reducing agent such as $NaCNBH_3$.

Listed below are definitions of various terms used to describe the compounds of the instant invention. These definitions apply to the terms as they are used throughout the specification (unless they are otherwise limited in specific instances) either individually or as part of a larger group.

The following abbreviations are employed herein:

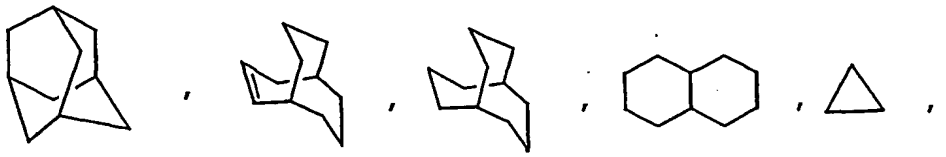
Ph = phenyl
Bn = benzyl
t-Bu = tertiary butyl
Me = methyl
Et = ethyl
TMS = trimethylsilyl
$TMSN_3$ = trimethylsilyl azide
TBS = tert-butyldimethylsilyl
THF = tetrahydrofuran
Et_2O = diethyl ether
EtOAc = ethyl acetate
DMF = dimethyl formamide
MeOH = methanol
EtOH = ethanol
i-PrOH = isopropanol
HOAc or AcOH = acetic acid
TFA = trifluoroacetic acid
$i\text{-}Pr_2NEt$ = diisopropylethylamine
Et_3N = triethylamine
DMAP = 4-dimethylaminopyridine
$NaBH_4$ = sodium borohydride
$LiAlH_4$ = lithium aluminum hydride

n-BuLi = n-butyllithium
Pd/C = palladium on carbon
KOH = potassium hydroxide
NaOH = sodium hydroxide
LiOH = lithium hydroxide
K_2CO_3 = potassium carbonate
$NaHCO_3$ = sodium bicarbonate
EDC (or EDC.HCl) or EDCI (or EDCI.HCl) or EDAC = 3-ethyl-3'-(dimethylamino)propyl- carbodiimide hydrochloride (or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride)
HOBT or HOBT.H_2O = 1-hydroxybenzotriazole hydrate
HOAT = 1-Hydroxy-7-azabenzotriazole
Ph_3P = triphenylphosphine
$Pd(OAc)_2$ = Palladium acetate
$(Ph_3P)_4Pd^o$ = tetrakis triphenylphosphine palladium
Ar = argon
N_2 = nitrogen
min = minute(s)
h or hr = hour(s)
L = liter
mL = milliliter
µL = microliter
g = gram(s)
mg = milligram(s)
mol = moles
mmol = millimole(s)
meq = milliequivalent
RT = room temperature
sat or sat'd = saturated
aq. = aqueous
TLC = thin layer chromatography
HPLC = high performance liquid chromatography
LC/MS = high performance liquid chromatography/mass spectrometry
MS or Mass Spec = mass spectrometry
NMR = nuclear magnetic resonance

mp = melting point
dppf = diphenylphosphinoferrocene
DCE = 1,2-dichloroethane

Unless otherwise indicated, the term "lower alkyl", "alkyl" or "alk" as employed herein alone or as part of another group includes both straight and branched chain hydrocarbons, containing 1 to 20 carbons, preferably 1 to 10 carbons, more preferably 1 to 8 carbons, in the normal chain, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl, the various branched chain isomers thereof, and the like as well as such groups including 1 to 4 substituents such as halo, for example F, Br, Cl or I or CF_3, alkyl, alkoxy, aryl, aryloxy, aryl(aryl) or diaryl, arylalkyl, arylalkyloxy, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkylalkyl, cycloalkylalkyloxy, optionally substituted amino, hydroxy, hydroxyalkyl, acyl, oxo, alkanoyl, heteroaryl, heteroaryloxy, cycloheteroalkyl, arylheteroaryl, arylalkoxycarbonyl, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, nitro, cyano, thiol, haloalkyl, trihaloalkyl and/or alkylthio.

Unless otherwise indicated, the term "cycloalkyl" as employed herein alone or as part of another group includes saturated or partially unsaturated (containing 1 or 2 double bonds) cyclic hydrocarbon groups containing 1 to 3 rings, including monocyclicalkyl, bicyclicalkyl and tricyclicalkyl, containing a total of 3 to 20 carbons forming the rings, preferably 3 to 10 carbons, forming the ring and which may be fused to 1 or 2 aromatic rings as described for aryl, which include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl and cyclododecyl, cyclohexenyl,



any of which groups may be optionally substituted with 1 to 4 substituents such as halogen, alkyl, alkoxy, hydroxy, aryl, aryloxy, arylalkyl, cycloalkyl, alkylamido, alkanoylamino, oxo, acyl, arylcarbonylamino, amino, nitro, cyano, thiol and/or alkylthio and/or any of the alkyl substituents.

The term "cycloalkenyl" as employed herein alone or as part of another group refers to cyclic hydrocarbons containing 3 to 12 carbons, preferably 5 to 10 carbons and 1 or 2 double bonds. Exemplary cycloalkenyl groups include cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclohexadienyl, and cycloheptadienyl, which may be optionally substituted as defined for cycloalkyl.

The term "alkanoyl" as used herein alone or as part of another group refers to alkyl linked to a carbonyl group.

Unless otherwise indicated, the term "lower alkenyl" or "alkenyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 20 carbons, preferably 2 to 12 carbons, and more preferably 1 to 8 carbons in the normal chain, which include one to six double bonds in the normal chain, such as vinyl, 2-propenyl, 3-butenyl, 2-butenyl, 4-pentenyl, 3-pentenyl, 2-hexenyl, 3-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 3-octenyl, 3-nonenyl, 4-decenyl, 3-undecenyl, 4-dodecenyl, 4,8,12-tetradecatrienyl, and the like, and which may be optionally substituted with 1 to 4 substituents, namely, halogen, haloalkyl, alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, amino, hydroxy, heteroaryl, cycloheteroalkyl, alkanoylamino, alkylamido, arylcarbonylamino, nitro,

cyano, thiol, alkylthio and/or any of the alkyl substituents set out herein.

Unless otherwise indicated, the term "lower alkynyl" or "alkynyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 20 carbons, preferably 2 to 12 carbons and more preferably 2 to 8 carbons in the normal chain, which include one triple bond in the normal chain, such as 2-propynyl, 3-butynyl, 2-butynyl, 4-pentynyl, 3-pentynyl, 2-hexynyl, 3-hexynyl, 2-heptynyl, 3-heptynyl, 4-heptynyl, 3-octynyl, 3-nonynyl, 4-decynyl,3-undecynyl, 4-dodecynyl and the like, and which may be optionally substituted with 1 to 4 substituents, namely, halogen, haloalkyl, alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, amino, heteroaryl, cycloheteroalkyl, hydroxy, alkanoylamino, alkylamido, arylcarbonylamino, nitro, cyano, thiol, and/or alkylthio, and/or any of the alkyl substituents set out herein.

The terms "arylakyl", "arylalkenyl" and "arylalkynyl" as used alone or as part of another group refer to alkyl, alkenyl and alkynyl groups as described above having an aryl substituent.

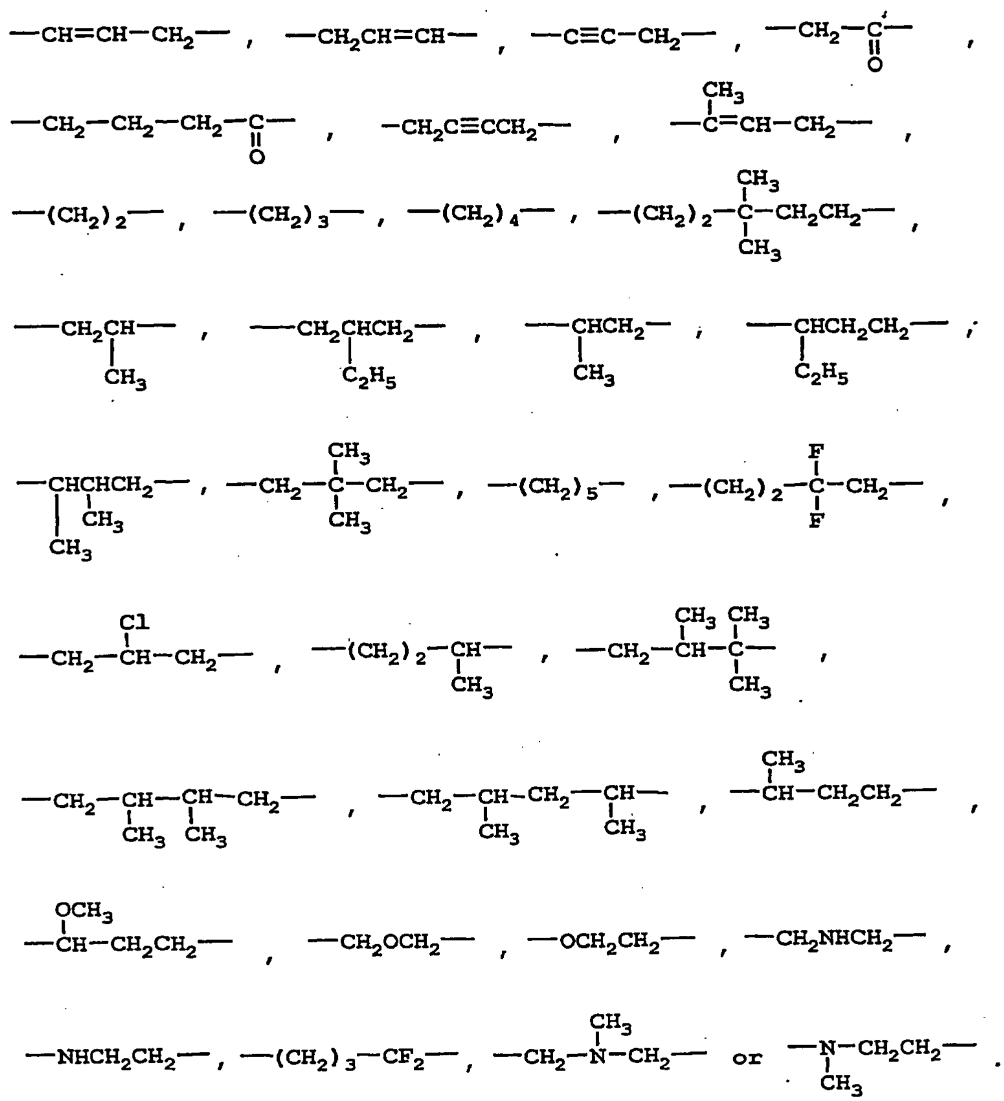
Where alkyl groups as defined above have single bonds for attachment to other groups at two different carbon atoms, they are termed "alkylene" groups and may optionally be substituted as defined above for "alkyl".

Where alkenyl groups as defined above and alkynyl groups as defined above, respectively, have single bonds for attachment at two different carbon atoms, they are termed "alkenylene groups" and "alkynylene groups", respectively, and may optionally be substituted as defined above for "alkenyl" and "alkynyl".

Suitable alkylene, alkenylene or alkynylene groups $(CH_2)_m$, $(CH_2)_n$ or $(CH_2)_p$ (where p can be 1 to 8, preferably 1 to 5, which includes alkylene, alkenylene or alkynylene groups as defined herein), may optionally include 1, 2, or 3 substituents which include alkyl,

alkenyl, halogen, cyano, hydroxy, alkoxy, amino, thioalkyl, keto, C_3-C_6 cycloalkyl, alkylcarbonylamino or alkylcarbonyloxy.

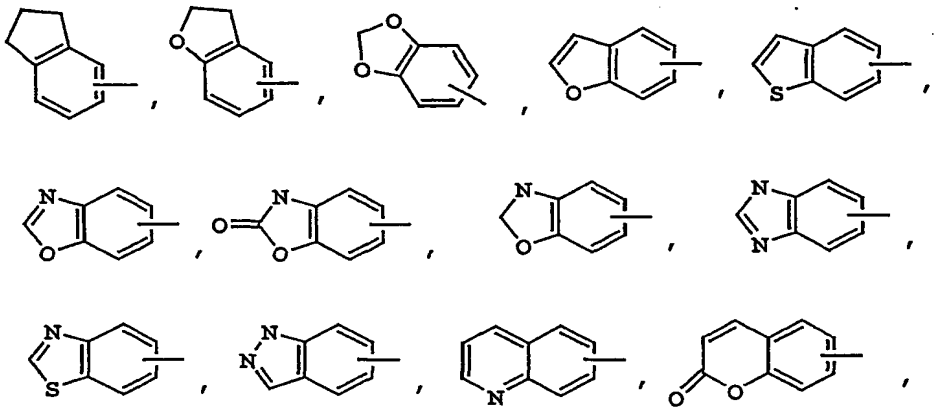
Examples of $(CH_2)_m$, $(CH_2)_n$ or $(CH_2)_p$, alkylene, alkenylene and alkynylene include $-CH_2-$, $-CH_2CH_2-$,



The term "halogen" or "halo" as used herein alone or as part of another group refers to chlorine, bromine, fluorine, and iodine, with chlorine or fluorine being preferred.

The term "metal ion" refers to alkali metal ions such as sodium, potassium or lithium and alkaline earth metal ions such as magnesium and calcium, as well as zinc and aluminum.

Unless otherwise indicated, the term "aryl" or "Aryl" as employed herein alone or as part of another group refers to monocyclic and bicyclic aromatic groups containing 6 to 10 carbons in the ring portion (such as phenyl or naphthyl including 1-naphthyl and 2-naphthyl) and may optionally include one to three additional rings fused to a carbocyclic ring or a heterocyclic ring (such as aryl, cycloalkyl, heteroaryl or cycloheteroalkyl rings for example



and may be optionally substituted through available carbon atoms with 1, 2, or 3 groups selected from hydrogen, halo, haloalkyl, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, trifluoromethyl, trifluoromethoxy, alkynyl, cycloalkyl-alkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, aryloxy, aryloxyalkyl, arylalkoxy, alkoxycarbonyl, arylcarbonyl, arylalkenyl, aminocarbonylaryl, arylthio, arylsulfinyl, arylazo, heteroarylalkyl, heteroarylalkenyl, heteroarylheteroaryl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino wherein the amino includes 1 or 2 substituents (which are alkyl, aryl or any of the other aryl compounds mentioned in the

definitions), thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkoxyarylthio, alkylcarbonyl, arylcarbonyl, alkylaminocarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonylamino or arylsulfonaminocarbonyl and/or any of the alkyl substituents set out herein.

Unless otherwise indicated, the term "lower alkoxy", "alkoxy", "aryloxy" or "aralkoxy" as employed herein alone or as part of another group includes any of the above alkyl, aralkyl or aryl groups linked to an oxygen atom.

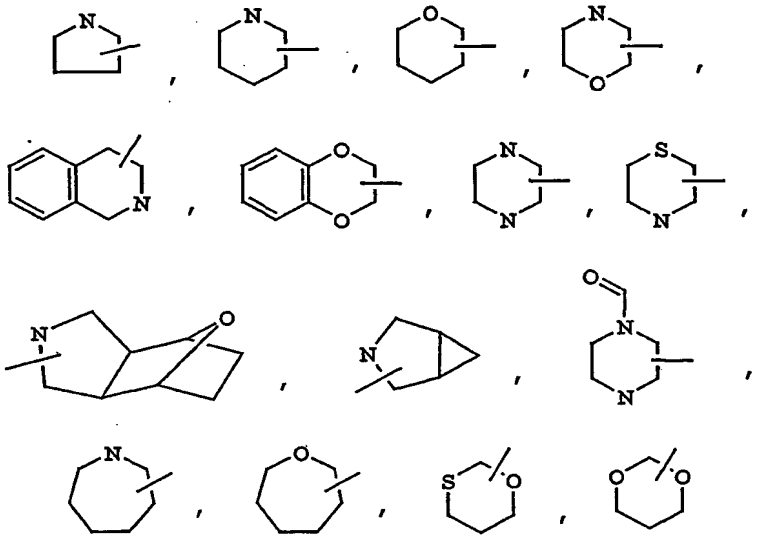
Unless otherwise indicated, the term "substituted amino" as employed herein alone or as part of another group refers to amino substituted with one or two substituents, which may be the same or different, such as alkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl or thioalkyl. These substituents may be further substituted with a carboxylic acid and/or any of the alkyl substituents as set out above. In addition, the amino substituents may be taken together with the nitrogen atom to which they are attached to form 1-pyrrolidinyl, 1-piperidinyl, 1-azepinyl, 4-morpholinyl, 4-thiamorpholinyl, 1-piperazinyl, 4-alkyl-1-piperazinyl, 4-arylalkyl-1-piperazinyl, 4-diarylalkyl-1-piperazinyl, 1-pyrrolidinyl, 1-piperidinyl, or 1-azepinyl, optionally substituted with alkyl, alkoxy, alkylthio, halo, trifluoromethyl or hydroxy.

Unless otherwise indicated, the term "lower alkylthio", alkylthio", "arylthio" or "aralkylthio" as employed herein alone or as part of another group includes any of the above alkyl, aralkyl or aryl groups linked to a sulfur atom.

Unless otherwise indicated, the term "lower alkylamino", "alkylamino", "arylamino", or "arylalkylamino" as employed herein alone or as part of another group includes any of the above alkyl, aryl or arylalkyl groups linked to a nitrogen atom.

Unless otherwise indicated, the term "acyl" as employed herein by itself or part of another group, as defined herein, refers to an organic radical linked to a carbonyl $\left(\begin{matrix}O\\ \|\\ C\end{matrix}\right)$ group; examples of acyl groups include any of the alkyl substituents attached to a carbonyl, such as alkanoyl, alkenoyl, aroyl, aralkanoyl, heteroaroyl, cycloalkanoyl, cycloheteroalkanoyl and the like.

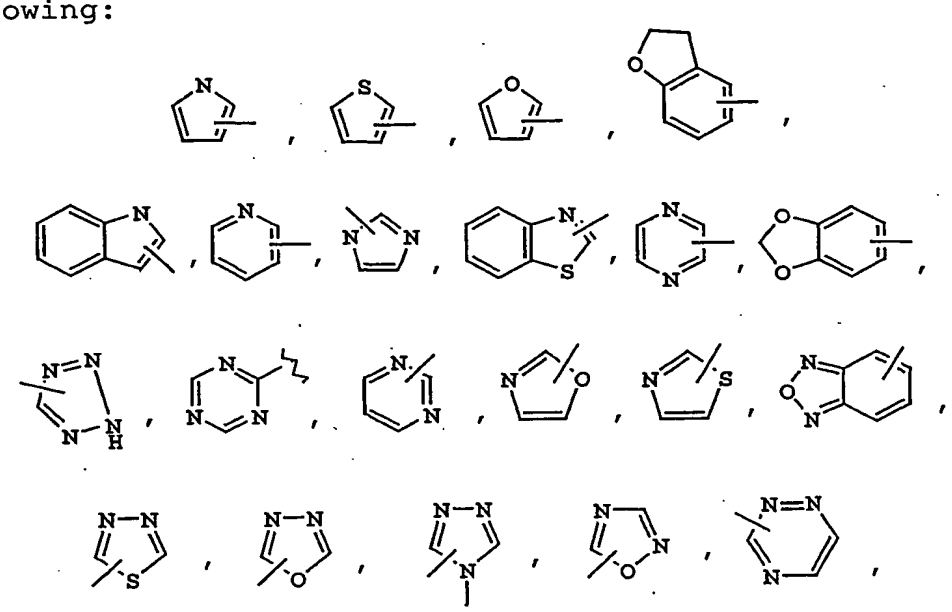
Unless otherwise indicated, the term "cycloheteroalkyl" as used herein alone or as part of another group refers to a 5-, 6- or 7-membered saturated or partially unsaturated ring which includes 1 to 2 hetero atoms such as nitrogen, oxygen and/or sulfur, linked through a carbon atom or a heteroatom, where possible, optionally via the linker $(CH_2)_p$ (where p is 1, 2 or 3), such as



and the like. The above groups may include 1 to 4 substituents such as alkyl, halo, oxo and/or any of of the alkyl substituents set out herein. In addition, any

of the cycloheteroalkyl rings can be fused to a cycloalkyl, aryl, heteroaryl or cycloheteroalkyl ring.

Unless otherwise indicated, the term "heteroaryl" as used herein alone or as part of another group refers to a 5- or 6- membered aromatic ring which includes 1, 2, 3 or 4 hetero atoms such as nitrogen, oxygen or sulfur, and such rings fused to an aryl, cycloalkyl, heteroaryl or cycloheteroalkyl ring (e.g. benzothiophenyl, indolyl), and includes possible N-oxides. The heteroaryl group may optionally include 1 to 4 substituents such as any of the the alkyl substituents set out above. Examples of heteroaryl groups include the following:



and the like.

The term "cycloheteroalkylalkyl" as used herein alone or as part of another group refers to cycloheteroalkyl groups as defined above linked through a C atom or heteroatom to a $(CH_2)_p$ chain.

The term "heteroarylalkyl" or "heteroarylalkenyl" as used herein alone or as part of another group refers to a heteroaryl group as defined above linked through a C atom or heteroatom to a $-(CH_2)_p-$ chain, alkylene or alkenylene as defined above.

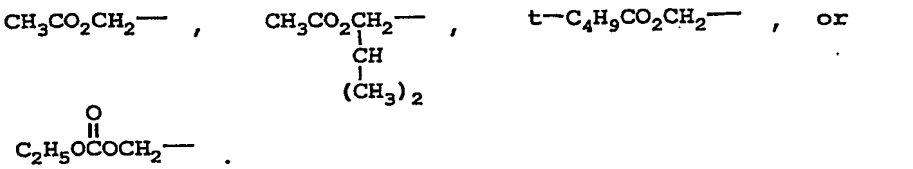
The term "five, six or seven membered carbocycle or heterocycle" as employed herein refers to cycloalkyl or cycloalkenyl groups as defined above or heteroaryl groups or cycloheteroaryl groups as defined above, such as thiadiazaole, tetrazole, imidazole, or oxazole.

The term "polyhaloalkyl" as used herein refers to an "alkyl" group as defined above which includes from 2 to 9, preferably from 2 to 5, halo substituents, such as F or Cl, preferably F, such as CF_3CH_2, CF_3 or $CF_3CF_2CH_2$.

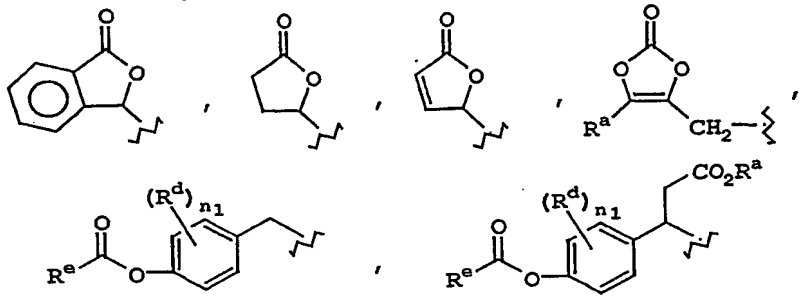
The term "polyhaloalkyloxy" as used herein refers to an "alkoxy" or "alkyloxy" group as defined above which includes from 2 to 9, preferably from 2 to 5, halo substituents, such as F or Cl, preferably F, such as CF_3CH_2O, CF_3O or $CF_3CF_2CH_2O$.

The term "prodrug esters" as employed herein includes esters and carbonates formed by reacting one or more hydroxyls of compounds of formula I with alkyl, alkoxy, or aryl substituted acylating agents employing procedures known to those skilled in the art to generate acetates, pivalates, methylcarbonates, benzoates and the like. In addition, prodrug esters which are known in the art for carboxylic and phosphorus acid esters such as methyl, ethyl, benzyl and the like.

Examples of such prodrug esters include



Other examples of suitable prodrug esters include



wherein R^a can be H, alkyl (such as methyl or t-butyl), arylalkyl (such as benzyl) or aryl (such as phenyl); R^d is H, alkyl, halogen or alkoxy, R^e is alkyl, aryl, arylalkyl or alkoxyl, and n_1 is 0, 1 or 2.

Where the compounds of structure I are in acid form they may form a pharmaceutically acceptable salt such as alkali metal salts such as lithium, sodium or potassium, alkaline earth metal salts such as calcium or magnesium as well as zinc or aluminum and other cations such as ammonium, choline, diethanolamine, lysine (D or L), ethylenediamine, t-butylamine, t-octylamine, tris-(hydroxymethyl)aminomethane (TRIS), N-methyl glucosamine (NMG), triethanolamine and dehydroabietylamine.

All stereoisomers of the compounds of the instant invention are contemplated, either in admixture or in pure or substantially pure form. The compounds of the present invention can have asymmetric centers at any of the carbon atoms including any one of the R substituents. Consequently, compounds of formula I can exist in enantiomeric or diastereomeric forms or in mixtures thereof. The processes for preparation can utilize racemates, enantiomers or diastereomers as starting materials. When diastereomeric or enantiomeric products are prepared, they can be separated by conventional methods for example, chromatographic or fractional crystallization.

Where desired, the compounds of structure I may be used in combination with one or more other types of antidiabetic agents and/or one or more other types of therapeutic agents which may be administered orally in the same dosage form, in a separate oral dosage form or by injection.

The other type of antidiabetic agent which may be optionally employed in combination with the SGLT2 inhibitor of formula I may be 1,2,3 or more antidiabetic agents or antihyperglycemic agents including insulin secretagogues or insulin sensitizers, or other

antidiabetic agents preferably having a mechanism of action different from SGLT2 inhibition and may include biguanides, sulfonyl ureas, glucosidase inhibitors, PPAR γ agonists, such as thiazolidinediones, aP2 inhibitors, PPAR α/γ dual agonists, dipeptidyl peptidase IV (DP4) inhibitors, and/or meglitinides, as well as insulin, and/or glucagon-like peptide-1 (GLP-1).

It is believed that the use of the compounds of structure I in combination with 1, 2, 3 or more other antidiabetic agents produces antihyperglycemic results greater than that possible from each of these medicaments alone and greater than the combined additive anti-hyperglycemic effects produced by these medicaments.

The other antidiabetic agent may be an oral antihyperglycemic agent preferably a biguanide such as metformin or phenformin or salts thereof, preferably metformin HCl.

Where the other antidiabetic agent is a biguanide, the compounds of structure I will be employed in a weight ratio to biguanide within the range from about 0.01:1 to about 100:1, preferably from about 0.1:1 to about 5:1.

The other antidiabetic agent may also preferably be a sulfonyl urea such as glyburide (also known as glibenclamide), glimepiride (disclosed in U.S. Patent No. 4,379,785), glipizide, gliclazide or chlorpropamide, other known sulfonylureas or other antihyperglycemic agents which act on the ATP-dependent channel of the β-cells, with glyburide and glipizide being preferred, which may be administered in the same or in separate oral dosage forms.

The compounds of structure I will be employed in a weight ratio to the sulfonyl urea in the range from about 0.01:1 to about 100:1, preferably from about 0.2:1 to about 10:1.

The oral antidiabetic agent may also be a glucosidase inhibitor such as acarbose (disclosed in U.S. Patent No. 4,904,769) or miglitol (disclosed in U.S.

Patent No. 4,639,436), which may be administered in the same or in a separate oral dosage forms.

The compounds of structure I will be employed in a weight ratio to the glucosidase inhibitor within the range from about 0.01:1 to about 100:1, preferably from about 0.5:1 to about 50:1.

The compounds of structure I may be employed in combination with a PPAR γ agonist such as a thiazolidinedione oral anti-diabetic agent or other insulin sensitizers (which has an insulin sensitivity effect in NIDDM patients) such as troglitazone (Warner-Lambert's Rezulin®, disclosed in U.S. Patent No. 4,572,912), rosiglitazone (SKB), pioglitazone (Takeda), Mitsubishi's MCC-555 (disclosed in U.S. Patent No. 5,594,016), Glaxo-Welcome's GL-262570, englitazone (CP-68722, Pfizer) or darglitazone (CP-86325, Pfizer, isaglitazone (MIT/J&J), JTT-501 (JPNT/P&U), L-895645 (Merck), R-119702 (Sankyo/WL), NN-2344 (Dr. Reddy/NN), or YM-440 (Yamanouchi), preferably rosiglitazone and pioglitazone.

The compounds of structure I will be employed in a weight ratio to the thiazolidinedione in an amount within the range from about 0.01:1 to about 100:1, preferably from about 0.2:1 to about 10:1.

The sulfonyl urea and thiazolidinedione in amounts of less than about 150 mg oral antidiabetic agent may be incorporated in a single tablet with the compounds of structure I.

The compounds of structure I may also be employed in combination with a antihyperglycemic agent such as insulin or with glucagon-like peptide-1 (GLP-1) such as GLP-1(1-36) amide, GLP-1(7-36) amide, GLP-1(7-37) (as disclosed in U.S. Patent No. 5,614,492 to Habener, the disclosure of which is incorporated herein by reference), as well as AC2993 (Amylen) and LY-315902 (Lilly), which may be administered via injection, intranasal, or by transdermal or buccal devices.

Where present, metformin, the sulfonyl ureas, such as glyburide, glimepiride, glipyride, glipizide, chlorpropamide and gliclazide and the glucosidase inhibitors acarbose or miglitol or insulin (injectable, pulmonary, buccal, or oral) may be employed in formulations as described above and in amounts and dosing as indicated in the Physician's Desk Reference (PDR).

Where present, metformin or salt thereof may be employed in amounts within the range from about 500 to about 2000 mg per day which may be administered in single or divided doses one to four times daily.

Where present, the thiazolidinedione anti-diabetic agent may be employed in amounts within the range from about 0.01 to about 2000 mg/day which may be administered in single or divided doses one to four times per day.

Where present insulin may be employed in formulations, amounts and dosing as indicated by the Physician's Desk Reference.

Where present GLP-1 peptides may be administered in oral buccal formulations, by nasal administration or parenterally as described in U.S. Patent Nos. 5,346,701 (TheraTech), 5,614,492 and 5,631,224 which are incorporated herein by reference.

The other antidiabetic agent may also be a PPAR α/γ dual agonist such as AR-HO39242 (Astra/Zeneca), GW-409544 (Glaxo-Wellcome), KRP297 (Kyorin Merck) as well as those disclosed by Murakami et al, "A Novel Insulin Sensitizer Acts As a Coligand for Peroxisome Proliferation - Activated Receptor Alpha (PPAR alpha) and PPAR gamma. Effect on PPAR alpha Activation on Abnormal Lipid Metabolism in Liver of Zucker Fatty Rats", Diabetes 47, 1841-1847 (1998), and in U.S. provisional application No. 60/155,400, filed September 22, 1999, (attorney file LA29) the disclosure of which is incorporated herein by reference, employing dosages as set out therein, which compounds designated as preferred are preferred for use herein.

The other antidiabetic agent may be an aP2 inhibitor such as disclosed in U.S. application Serial No. 09/391,053, filed September 7, 1999, and in U.S. provisional application No. 60/127,745, filed April 5, 1999 (attorney file LA27*), employing dosages as set out herein. Preferred are the compounds designated as preferred in the above application.

The other antidiabetic agent may be a DP4 inhibitor such as disclosed in WO99/38501, WO99/46272, WO99/67279 (PROBIODRUG), WO99/67278 (PROBIODRUG), WO99/61431 (PROBIODRUG), NVP-DPP728A (1-[[[2-[(5-cyanopyridin-2-yl)amino]ethyl]amino]acetyl]-2-cyano-(S)-pyrrolidine) (Novartis) (preferred) as disclosed by Hughes et al, Biochemistry, 38(36), 11597-11603, 1999, TSL-225 (tryptophyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (disclosed by Yamada et al, Bioorg. & Med. Chem. Lett. 8 (1998) 1537-1540, 2-cyanopyrrolidides and 4-cyanopyrrolidides as disclosed by Ashworth et al, Bioorg. & Med. Chem. Lett., Vol. 6, No. 22, pp 1163-1166 and 2745-2748 (1996) employing dosages as set out in the above references.

The meglitinide which may optionally be employed in combination with the compound of formula I of the invention may be repaglinide, nateglinide (Novartis) or KAD1229 (PF/Kissei), with repaglinide being preferred.

The SGLT2 inhibitor of formula I will be employed in a weight ratio to the meglitinide, PPAR γ agonist, PPAR α/γ dual agonist, aP2 inhibitor or DP4 inhibitor within the range from about 0.01:1 to about 100:1, preferably from about 0.2:1 to about 10:1.

The hypolipidemic agent or lipid-lowering agent which may be optionally employed in combination with the compounds of formula I of the invention may include 1,2,3 or more MTP inhibitors, HMG CoA reductase inhibitors, squalene synthetase inhibitors, fibric acid derivatives, ACAT inhibitors, lipoxygenase inhibitors, cholesterol absorption inhibitors, ileal Na^+/bile acid cotransporter

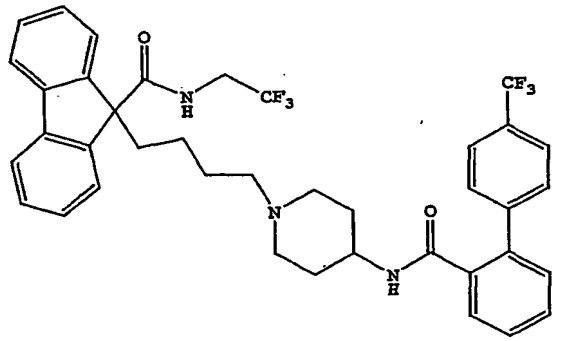
inhibitors, upregulators of LDL receptor activity, bile acid sequestrants, and/or nicotinic acid and derivatives thereof.

MTP inhibitors employed herein include MTP inhibitors disclosed in U.S. Patent No. 5,595,872, U.S. Patent No. 5,739,135, U.S. Patent No. 5,712,279, U.S. Patent No. 5,760,246, U.S. Patent No. 5,827,875, U.S. Patent No. 5,885,983 and U.S. Application Serial No. 09/175,180 filed October 20, 1998, now U.S. Patent No. 5,962,440. Preferred are each of the preferred MTP inhibitors disclosed in each of the above patents and applications.

All of the above U.S. Patents and applications are incorporated herein by reference.

Most preferred MTP inhibitors to be employed in accordance with the present invention include preferred MTP inhibitors as set out in U.S. Patent Nos. 5,739,135 and 5,712,279, and U.S. Patent No. 5,760,246.

The most preferred MTP inhibitor is 9-[4-[4-[[2-(2,2,2-Trifluoroethoxy)benzoyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide



The hypolipidemic agent may be an HMG CoA reductase inhibitor which includes, but is not limited to, mevastatin and related compounds as disclosed in U.S. Patent No. 3,983,140, lovastatin (mevinolin) and related compounds as disclosed in U.S. Patent No. 4,231,938, pravastatin and related compounds such as disclosed in U.S. Patent No. 4,346,227, simvastatin and related

compounds as disclosed in U.S. Patent Nos. 4,448,784 and 4,450,171. Other HMG CoA reductase inhibitors which may be employed herein include, but are not limited to, fluvastatin, disclosed in U.S. Patent No. 5,354,772, cerivastatin disclosed in U.S. Patent Nos. 5,006,530 and 5,177,080, atorvastatin disclosed in U.S. Patent Nos. 4,681,893, 5,273,995, 5,385,929 and 5,686,104, atavastatin (Nissan/Sankyo's nisvastatin (NK-104)) disclosed in U.S. Patent No. 5,011,930, Shionogi-Astra/Zeneca visastatin (ZD-4522) disclosed in U.S. Patent No. 5,260,440, and related statin compounds disclosed in U.S. Patent No. 5,753,675, pyrazole analogs of mevalonolactone derivatives as disclosed in U.S. Patent No. 4,613,610, indene analogs of mevalonolactone derivatives as disclosed in PCT application WO 86/03488, 6-[2-(substituted-pyrrol-1-yl)-alkyl]pyran-2-ones and derivatives thereof as disclosed in U.S. Patent No. 4,647,576, Searle's SC-45355 (a 3-substituted pentanedioic acid derivative) dichloroacetate, imidazole analogs of mevalonolactone as disclosed in PCT application WO 86/07054, 3-carboxy-2-hydroxy-propane-phosphonic acid derivatives as disclosed in French Patent No. 2,596,393, 2,3-disubstituted pyrrole, furan and thiophene derivatives as disclosed in European Patent Application No. 0221025, naphthyl analogs of mevalonolactone as disclosed in U.S. Patent No. 4,686,237, octahydronaphthalenes such as disclosed in U.S. Patent No. 4,499,289, keto analogs of mevinolin (lovastatin) as disclosed in European Patent Application No.0,142,146 A2, and quinoline and pyridine derivatives disclosed in U.S. Patent No. 5,506,219 and 5,691,322.

In addition, phosphinic acid compounds useful in inhibiting HMG CoA reductase suitable for use herein are disclosed in GB 2205837.

The squalene synthetase inhibitors suitable for use herein include, but are not limited to, α-phosphono-sulfonates disclosed in U.S. Patent No. 5,712,396, those

disclosed by Biller et al, J. Med. Chem., 1988, Vol. 31, No. 10, pp 1869-1871, including isoprenoid (phosphinylmethyl)phosphonates as well as other known squalene synthetase inhibitors, for example, as disclosed in U.S. Patent No. 4,871,721 and 4,924,024 and in Biller, S.A., Neuenschwander, K., Ponpipom, M.M., and Poulter, C.D., Current Pharmaceutical Design, 2, 1-40 (1996).

In addition, other squalene synthetase inhibitors suitable for use herein include the terpenoid pyrophosphates disclosed by P. Ortiz de Montellano et al, J. Med. Chem., 1977, 20, 243-249, the farnesyl diphosphate analog A and presqualene pyrophosphate (PSQ-PP) analogs as disclosed by Corey and Volante, J. Am. Chem. Soc., 1976, 98, 1291-1293, phosphinylphosphonates reported by McClard, R.W. et al, J.A.C.S., 1987, 109, 5544 and cyclopropanes reported by Capson, T.L., PhD dissertation, June, 1987, Dept. Med. Chem. U of Utah, Abstract, Table of Contents, pp 16, 17, 40-43, 48-51, Summary.

Other hypolipidemic agents suitable for use herein include, but are not limited to, fibric acid derivatives, such as fenofibrate, gemfibrozil, clofibrate, bezafibrate, ciprofibrate, clinofibrate and the like, probucol, and related compounds as disclosed in U.S. Patent No. 3,674,836, probucol and gemfibrozil being preferred, bile acid sequestrants such as cholestyramine, colestipol and DEAE-Sephadex (Secholex®, Policexide®), as well as lipostabil (Rhone-Poulenc), Eisai E-5050 (an N-substituted ethanolamine derivative), imanixil (HOE-402), tetrahydrolipstatin (THL), istigmastanylphosphorylcholine (SPC, Roche), aminocyclodextrin (Tanabe Seiyoku), Ajinomoto AJ-814 (azulene derivative), melinamide (Sumitomo), Sandoz 58-035, American Cyanamid CL-277,082 and CL-283,546 (disubstituted urea derivatives), nicotinic acid, acipimox, acifran, neomycin, p-aminosalicylic acid, aspirin, poly(diallylmethylamine) derivatives such as disclosed in

U.S. Patent No. 4,759,923, quaternary amine poly(diallyldimethylammonium chloride) and ionenes such as disclosed in U.S. Patent No. 4,027,009, and other known serum cholesterol lowering agents.

The other hypolipidemic agent may be an ACAT inhibitor such as disclosed in, Drugs of the Future 24, 9-15 (1999), (Avasimibe); "The ACAT inhibitor, Cl-1011 is effective in the prevention and regression of aortic fatty streak area in hamsters", Nicolosi et al, Atherosclerosis (Shannon, Irel). (1998), 137(1), 77-85; "The pharmacological profile of FCE 27677: a novel ACAT inhibitor with potent hypolipidemic activity mediated by selective suppression of the hepatic secretion of ApoB100-containing lipoprotein", Ghiselli, Giancarlo, Cardiovasc. Drug Rev. (1998), 16(1), 16-30; "RP 73163: a bioavailable alkylsulfinyl-diphenylimidazole ACAT inhibitor", Smith, C., et al, Bioorg. Med. Chem. Lett. (1996), 6(1), 47-50; "ACAT inhibitors: physiologic mechanisms for hypolipidemic and anti-atherosclerotic activities in experimental animals", Krause et al, Editor(s): Ruffolo, Robert R., Jr.; Hollinger, Mannfred A., Inflammation: Mediators Pathways (1995), 173-98, Publisher: CRC, Boca Raton, Fla.; "ACAT inhibitors: potential anti-atherosclerotic agents", Sliskovic et al, Curr. Med. Chem. (1994), 1(3), 204-25; "Inhibitors of acyl-CoA:cholesterol O-acyl transferase (ACAT) as hypocholesterolemic agents. 6. The first water-soluble ACAT inhibitor with lipid-regulating activity. Inhibitors of acyl-CoA:cholesterol acyltransferase (ACAT). 7. Development of a series of substituted N-phenyl-N'-[(1-phenylcyclopentyl)methyl]ureas with enhanced hypocholesterolemic activity", Stout et al, Chemtracts: Org. Chem. (1995), 8(6), 359-62, or TS-962 (Taisho Pharmaceutical Co. Ltd).

The hypolipidemic agent may be an upregulator of LD2 receptor activity such as MD-700 (Taisho Pharmaceutical Co. Ltd) and LY295427 (Eli Lilly).

The hypolipidemic agent may be a cholesterol absorption inhibitor preferably Schering-Plough's SCH48461 as well as those disclosed in Atherosclerosis 115, 45-63 (1995) and J. Med. Chem. 41, 973 (1998).

The hypolipidemic agent may be an ileal Na^+/bile acid cotransporter inhibitor such as disclosed in Drugs of the Future, 24, 425-430 (1999).

Preferred hypolipidemic agents are pravastatin, lovastatin, simvastatin, atorvastatin, fluvastatin, cerivastatin, atavastatin and ZD-4522.

The above-mentioned U.S. patents are incorporated herein by reference. The amounts and dosages employed will be as indicated in the Physician's Desk Reference and/or in the patents set out above.

The compounds of formula I of the invention will be employed in a weight ratio to the hypolipidemic agent (were present), within the range from about 500:1 to about 1:500, preferably from about 100:1 to about 1:100.

The dose administered must be carefully adjusted according to age, weight and condition of the patient, as well as the route of administration, dosage form and regimen and the desired result.

The dosages and formulations for the hypolipidemic agent will be as disclosed in the various patents and applications discussed above.

The dosages and formulations for the other hypolipidemic agent to be employed, where applicable, will be as set out in the latest edition of the Physicians' Desk Reference.

For oral administration, a satisfactory result may be obtained employing the MTP inhibitor in an amount within the range of from about 0.01 mg/kg to about 500 mg and preferably from about 0.1 mg to about 100 mg, one to four times daily.

A preferred oral dosage form, such as tablets or capsules, will contain the MTP inhibitor in an amount of from about 1 to about 500 mg, preferably from about 2 to

about 400 mg, and more preferably from about 5 to about 250 mg, one to four times daily.

For oral administration, a satisfactory result may be obtained employing an HMG CoA reductase inhibitor, for example, pravastatin, lovastatin, simvastatin, atorvastatin, fluvastatin or cerivastatin in dosages employed as indicated in the Physician's Desk Reference, such as in an amount within the range of from about 1 to 2000 mg, and preferably from about 4 to about 200 mg.

The squalene synthetase inhibitor may be employed in dosages in an amount within the range of from about 10 mg to about 2000 mg and preferably from about 25 mg to about 200 mg.

A preferred oral dosage form, such as tablets or capsules, will contain the HMG CoA reductase inhibitor in an amount from about 0.1 to about 100 mg, preferably from about 5 to about 80 mg, and more preferably from about 10 to about 40 mg.

A preferred oral dosage form, such as tablets or capsules will contain the squalene synthetase inhibitor in an amount of from about 10 to about 500 mg, preferably from about 25 to about 200 mg.

The other hypolipidemic agent may also be a lipoxygenase inhibitor including a 15-lipoxygenase (15-LO) inhibitor such as benzimidazole derivatives as disclosed in WO 97/12615, 15-LO inhibitors as disclosed in WO 97/12613, isothiazolones as disclosed in WO 96/38144, and 15-LO inhibitors as disclosed by Sendobry et al "Attenuation of diet-induced atherosclerosis in rabbits with a highly selective 15-lipoxygenase inhibitor lacking significant antioxidant properties", Brit. J. Pharmacology (1997) 120, 1199-1206, and Cornicelli et al, "15-Lipoxygenase and its Inhibition: A Novel Therapeutic Target for Vascular Disease", Current Pharmaceutical Design, 1999, 5, 11-20.

The compounds of formula I and the hypolipidemic agent may be employed together in the same oral dosage

form or in separate oral dosage forms taken at the same time.

The compositions described above may be administered in the dosage forms as described above in single or divided doses of one to four times daily. It may be advisable to start a patient on a low dose combination and work up gradually to a high dose combination.

The preferred hypolipidemic agent is pravastatin, simvastatin, lovastatin, atorvastatin, fluvastatin or cerivastatin.

The other type of therapeutic agent which may be optionally employed with the SGLT2 inhibitor of formula I may be 1, 2, 3 or more of an anti-obesity agent including a beta 3 adrenergic agonist, a lipase inhibitor, a serotonin (and dopamine) reuptake inhibitor, a thyroid receptor beta drug and/or an anorectic agent.

The beta 3 adrenergic agonist which may be optionally employed in combination with a compound of formula I may be AJ9677 (Takeda/Dainippon), L750355 (Merck), or CP331648 (Pfizer) or other known beta 3 agonists as disclosed in U.S. Patent Nos. 5,541,204, 5,770,615, 5,491,134, 5,776,983 and 5,488,064, with AJ9677, L750,355 and CP331648 being preferred.

The lipase inhibitor which may be optionally employed in combination with a compound of formula I may be orlistat or ATL-962 (Alizyme), with orlistat being preferred.

The serotonin (and dopoamine) reuptake inhibitor which may be optionally employed in combination with a compound of formula I may be sibutramine, topiramate (Johnson & Johnson) or axokine (Regeneron), with sibutramine and topiramate being preferred.

The thyroid receptor beta compound which may be optionally employed in combination with a compound of formula I may be a thyroid receptor ligand as disclosed in WO97/21993 (U. Cal SF), WO99/00353 (KaroBio) and

GB98/284425 (KaroBio), with compounds of the KaroBio applications being preferred.

The anorectic agent which may be optionally employed in combination with a compound of formula I may be dexamphetamine, phentermine, phenylpropanolamine or mazindol, with dexamphetamine being preferred.

The various anti-obesity agents described above may be employed in the same dosage form with the compound of formula I or in different dosage forms, in dosages and regimens as generally known in the art or in the PDR.

In carrying out the method of the invention for treating diabetes and related diseases, a pharmaceutical composition will be employed containing the compounds of structure I, with or without other antidiabetic agent(s) and/or antihyperlipidemic agent(s) and/or other type therapeutic agents in association with a pharmaceutical vehicle or diluent. The pharmaceutical composition can be formulated employing conventional solid or liquid vehicles or diluents and pharmaceutical additives of a type appropriate to the mode of desired administration, such as pharmaceutically acceptable carriers, excipients, binders and the like. The compounds can be administered to mammalian species including humans, monkeys, dogs, etc. by an oral route, for example, in the form of tablets, capsules, beads, granules or powders, or they can be administered by a parenteral route in the form of injectable preparations, or they can be administered intranasally or in transdermal patches. Typical solid formulations will contain from about 10 to about 500 mg of a compound of formula I. The dose for adults is preferably between 10 and 2,000 mg per day, which can be administered in a single dose or in the form of individual doses from 1-4 times per day.

A typical injectable preparation is produced by aseptically placing 250 mg of compounds of structure I into a vial, aseptically freeze-drying and sealing. For use, the contents of the vial are mixed with 2 mL of

physiological saline, to produce an injectable preparation.

SGLT2 inhibitor activity of the compounds of the invention may be determined by use of an assay system as set out below.

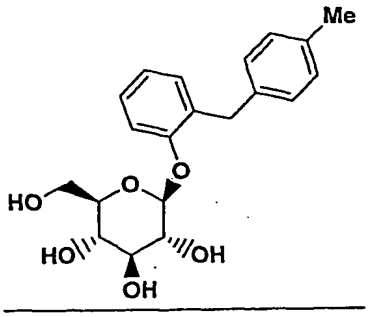
Assay for SGLT2 Activity

The mRNA sequence for human SGLT2 (GenBank #M95549) was cloned by reverse-transcription and amplification from human kidney mRNA, using standard molecular biology techniques. The cDNA sequence was stably transfected into CHO cells, and clones were assayed for SGLT2 activity essentially as described in Ryan et al. (1994). Evaluation of inhibition of SGLT2 activity in a clonally selected cell line was performed essentially as described in Ryan et al., with the following modifications. Cells were grown in 96-well plates for 2-4 days to 75,000 or 30,000 cells per well in F-12 nutrient mixture (Ham's F-12), 10% fetal bovine serum, 300 ug/ml Geneticin and penicillin-streptomycin. At confluence, cells were washed twice with 10 mM Hepes/Tris, pH 7.4, 137 mM N-methyl-D-glucamine, 5.4 mM KCl, 2.8 mM $CaCl_2$, 1.2 mM $MgSO_4$. Cells then were incubated with 10 µM [^{14}C]AMG, and 10 µM inhibitor (final DMSO =0.5%) in 10 mM Hepes/Tris, pH 7.4, 137 mM NaCl, 5.4 mM KCl, 2.8 mM $CaCl_2$, 1.2 mM $MgSO_4$ at 37^{0}C for 1.5 hr. Uptake assays were quenched with ice cold 1X PBS containing 0.5 mM phlorizin, and cells were then lysed with 0.1% NaOH. After addition of MicroScint scintillation fluid, the cells were allowed to shake for 1 hour, and then [^{14}C]AMG was quantitated on a TopCount scintillation counter. Controls were performed with and without NaCl. For determination of EC_{50} values, 10 inhibitor concentrations were used over 2 log intervals in the appropriate response range, and triplicate plates were averaged across plates.

Ryan MJ, Johnson G, Kirk J, Fuerstenberg SM, Zager RA and Torok-Storb B. **1994**. HK-2: an immortalized proximal tubule epithelial cell line from normal adult human kidney. Kidney International **45**: 48-57.

The following Working Examples represent preferred embodiments of the present invention. All temperatures are expressed in degrees Centigrade unless otherwise indicated.

Example 1



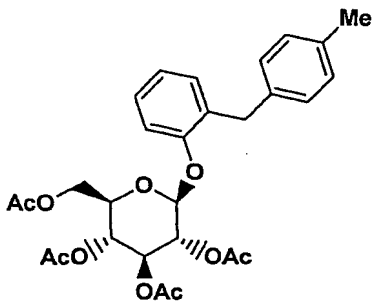
A. 4-Methyl-2'-hydroxybenzhydrol

To a 500ml round bottom flask containing 100 mL of THF under Ar was added commercial 1 M *p*-methylphenyl magnesium bromide/Et_2O (100 mL, 100 mmol). Subsequently, salicylaldehyde (4.9 g, 40.3 mmol) was added dropwise in four equal portions spaced over 2 hr. After 20 min, once HPLC analysis revealed the aldehyde to be consumed, the reaction was quenched by dropwise addition of 26 ml of sat'd NH_4Cl/H_2O to produce a white paste. To this suspension was added 200 mL of PhMe and sufficient H_2O to permit stirring. The organic layer was decanted whereupon the white paste was triterated a second time with 1:1 THF/PhMe. After decanting, the combined organic layers were concentrated using a rotary evaporator to obtain 9.7 g of crude 4-methyl-2'-hydroxybenzhydrol.

B. 2-(4'-Methylbenzyl)phenol

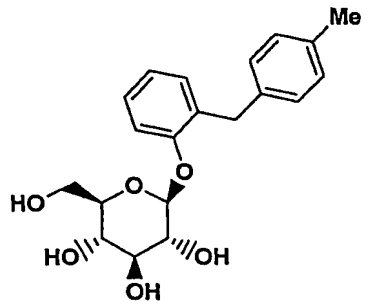
To a solution of crude Part A 4-methyl-2'-hydroxybenzhydrol (9.7 g containing no more than 40 mmol) in 175 mL of MeOH was added 0.59 g of 10% Pd/C and 1.75 mL of TFA. The suspension was stirred for 40 hr under 1 atmos. H_2, filtered through celite and concentrated to yield 8.6 of crude 2-(4'-methylbenzyl)phenol as an oil.

C.



A mixture of Part B 2-(p-methylbenzyl)phenol (8.6 g, containing no more than 37 mmol), 2,6-di-*t*-butyl-4-methylpyridine (10.6 g, 52 mmol), 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide (17.5 g, 43 mmol) in 270 mL CH_2Cl_2 was stirred until homogeneous prior to cooling to 0°. After addition of AgOTf (12.2 g, 47 mmol) to the cold solution, the reaction was stirred 1 hr prior to addition of additional 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide (7.6 g, 18 mmol) and AgOTf (6.5 g, 25 mmol). An additional 100 mL of CH_2Cl_2 was required to dilute the suspension to maintain stirring. After 30 min, the suspension was directly loaded on a silica gel column which was eluted initially with 25% EtOAc/hexane. The undesired minor α anomeric product eluted first followed by desired title β-O-glucoside tetraacetate as the eluant increased from 25-35% EtOAc/hexane. After concentration, the crude product, dissolved in the minimum EtOAc, was induced to crystallize by addition of hexane. A total of 8.25 g of pure desired title beta isomer plus ~3 g of impure material was obtained.

D.



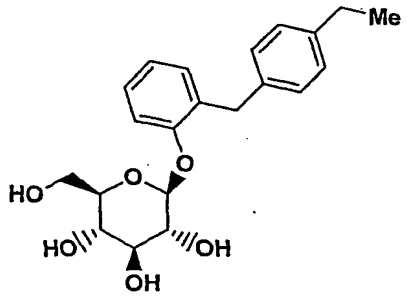
To a solution of Part C compound (8.25 g, 15 mmol) in 35 mL of CH_2Cl_2 was added MeOH (200 mL) followed by 0.7 mL of 1 N NaOH in H_2O. After 2 hr, when the reaction was complete as determined by HPLC, the volatiles were removed using a rotary evaporator. The residue, dissolved in a 1:10:10 mixture of H_2O/CH_2Cl_2/MeOH (42 mL), was diluted with CH_2Cl_2 (400 mL) and subsequently loaded onto a silica gel column. The desired product (5.68 g), after elution with 5-7% of MeOH/CH_2Cl_2 and removal of the volatiles, was isolated as a white solid.

^{1}H NMR (400 MHz, CD_3OD) δ 7.15-7.08 (m, 4H), 7.05 (m, 3H), 6.91 (m,1H),4.93 (d, 1H,obscured), 4.04 (d, 1H, J=14 Hz), 3.95 (d, 1H, J=14 Hz), 3.88 (d, 1H, J=12 Hz), 3.68 (dd, 1H, J=12, 3 Hz), 3.52-3.36 (m, 4H), 2.27 (s, 3H).

HPLC retention time: 6.88 min, Zorbax C-18 4.6x75mm, 2.5 mL/min, detection at 220 nm, 8 min gradient 0-100% B hold 3 min at 100% B. Solvent A: 10% MeOH/H_2O + 0.2 % H_3PO_4. Solvent B: 90% MeOH/H_2O + 0.2 % H_3PO_4.

Anal Calcd for $C_{20}H_{24}O_6$ LC-MS (M+Na) 383

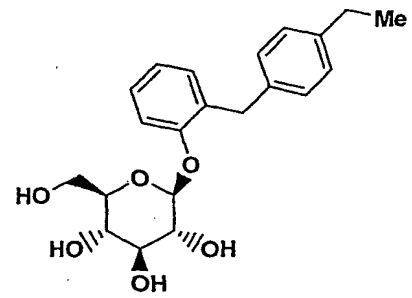
Example 2



A. 2-(4'-Ethylbenzyl)phenol

A 60% dispersion of NaH/mineral oil (144 mg, 3.6 mmol) under Ar was added dropwise to a stirred solution of phenol (284 mg, 3 mmol) in PhMe (15 mL). After 10 min, *p*-ethylbenzyl chloride (1.23 g, 5.3 mmol) in PhMe (2 mL) was added prior to heating the reaction for 6 hr at 80°. After cooling, the volatiles were removed using a rotary evaporator and the residue dissolved in 15 mL of MeOH. The MeOH solution was extracted 4 x with hexane prior to concentration. The resulting residue was dissolved in 1:1 EtOAc/H_2O (100 mL), the pH adjusted to 5 and the two phases separated. After drying over Na_2SO_4 and removal of the EtOAc, 390 mg of crude title 2-(4'-ethylbenzyl)phenol was obtained. Prep HPLC yielded 275 mg of clean 2-(4'-ethylbenzyl)phenol.

B.



A suspension of 2-(4'-ethylbenzyl)phenol (212 mg, 1 mmol), 2,3,4,6-tetra -O-acetyl- α -D-glucopyranosyl bromide (822 mg, 2 mmol), and Ag_2O (232 mg, 2 mmol) in 4 mL lutidine was stirred for 14 hr at 20°. Since the conversion was 80% complete by HPLC, an additional

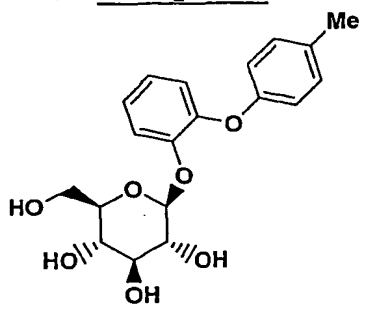
2,3,4,6-tetra -O-acetyl- α -D-glucopyranosyl bromide (411 mg, 1 mmol) and Ag_2O (116 mg, 1 mmol) was added and the reaction continued for 24 hr. Afterwards, H_2O (5 mL) and 1N aq. NaOH (2 mL) was added and the suspension stirred for 16 hr. The reaction mixture was extracted twice with EtOAc. The EtOAc extracts were dried over Na_2SO_4 before concentration. The resulting residue was purified by Prep HPLC to yield 8.7 mg of final product.

^1H NMR (400 MHz, CD_3OD) δ 7.15 (m, 4H), 7.08-7.01 (m, 3H), 6.91 (m,1H), 4.91 (d, 1H, obscured), 4.08 (d, 1H, J=14 Hz), 3.95 (d, 1H, J=14 Hz), 3.88 (d, 1H, J=12 Hz), 3.68 (dd, 1H, J=12, 3 Hz), 3.53-3.37 (m, 4H), 2.57 (q, 2H, J=7Hz), 1.18 (t, 3H, J=7Hz).

HPLC retention time: 7.32 min, Zorbax C-18 4.6x75mm, 2.5 mL/min, detection at 220 nm, 8 min gradient 0-100% B hold 3 min at 100% B. Solvent A: 10% MeOH/H_2O + 0.2 % H_3PO_4. Solvent B: 90% MeOH/H_2O + 0.2 % H_3PO_4.

Anal Calcd for $C_{21}H_{26}O_6$ LC-MS (M+Na) 397

Example 3



A. 2-Benzyloxy-4'-methyldiphenyl ether

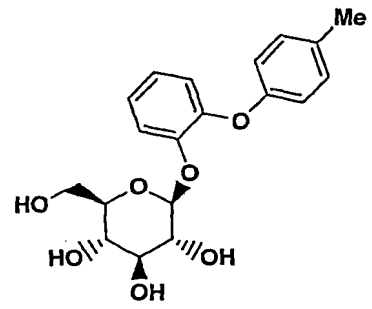
A mixture of 2-benzyloxyphenol (5 g, 2.49 mmol), $Cu(OAc)_2$ (452 mg, 2.49 mmol), *p*-methylphenylboronic acid (339 mg, 2.49 mmol), and activated 4A° molecular sieves (10 g) in CH_2Cl_2 (8 mL) was stirred for a few minutes prior to the addition of Et_3N (1.26g, 12.5 mmol) followed by pyridine (0.99 g, 12.5 mmol. After stirring for 20

hr, the reaction was filtered through celite which was washed with CH_2Cl_2. The filtrate was concentrated and the residue chromatographed on silica gel using 4% EtOAc/hexane to elute 280 mg (39%) of the desired title 2-benzyloxy-4'-methyldiphenyl ether.

B. 2-Hydroxy-4'-methyldiphenyl ether

A solution of Part A compound (280 mg, 0.96 mmol) in MeOH (50 mL) over Pd/C (30 mg) was stirred overnight under 1 atmosphere of H_2. The reaction was filtered through celite which was subsequently washed with MeOH and CH_2Cl_2. Removal of the solvent yielded 190 mg of title 2-hydroxy-4'-methyldiphenyl ether.

C.



A suspension comprised of Part B compound (94 mg, 0.47 mmol), 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide (185 mg, 0.45 mmol),and Ag_2O (62 mg, 0.27 mmol) in 1.0 mL lutidine was stirred for 19 hr at 65°. Since the reaction was 50% complete by HPLC analysis, additional 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide (185 mg, 0.45 mmol) and Ag_2O (62 mg, 0.27 mmol) were added and the reaction continued for 3 more hours. After cooling, 1 N HCl (25 mL) was added prior to 3 EtOAc extractions (total volume 75 mL). The combined organic extracts were washed with H_2O, aq. $NaHCO_3$, and brine prior to drying over $MgSO_4$. After removal of the solvent under vacuum, 50 mg of crude product was obtained. Without purification, this material was stirred overnight in 1:2:3 H_2O/THF/MeOH (1 mL) containing LiOH (4.7 mg, 0.17 mmol). The

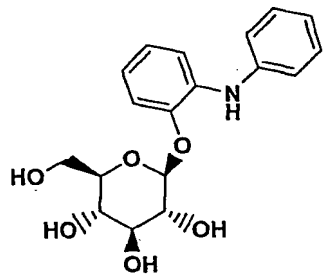
volatiles were removed and the residue was purified by Prep HPLC. A 10 min. gradient elution (30% to 90% MeOH/H_2O) from a YMC S5 C18 reverse phase column eluted 26 mg of final O-glucoside after lyophilization.

^1H NMR (400 MHz, CD_3OD) δ 2.29 (s, 3 H), 3.34-3.42 (m, 4 H), 3.67 (dd, 1H, J = 4.8, 11.3 Hz), 3.85 (dd, 1H, J = 2.2, 11.9 Hz), 4.95 (d, 1H, J = 7.0 Hz), 6.82-7.29 (m, 8 H).

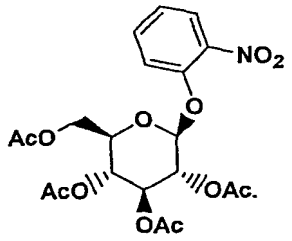
HPLC retention time: 6.47 min, 93% purity, Zorbax C-18 4.6x75mm, 2.5 mL/min, detection at 220 nm, 8 min gradient 0-100% B hold 3 min at 100% B. Solvent A: 10% MeOH/H_2O + 0.2% H_3PO_4. Solvent B: 90% MeOH/H_2O + 0.2% H_3PO_4.

Anal Calcd for $C_{19}H_{22}O_7$, Low Res. MS [M+Na] = 385, [M + NH4] = 380, [2M+ NH4] = 742, [M-H] = 361, [2M-H] = 723.

Example 4



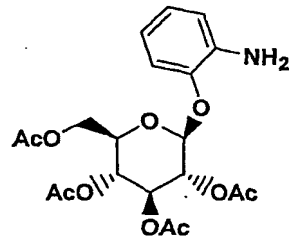
A.



A suspension of 2-nitrophenol (1.67 g, 12 mmol), 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide (4.5 g, 10.9 mmol), and Ag_2O (1.6 g, 7.1 mmol) in 20 mL lutidine was stirred for 19 hr at 20°. The reaction was diluted

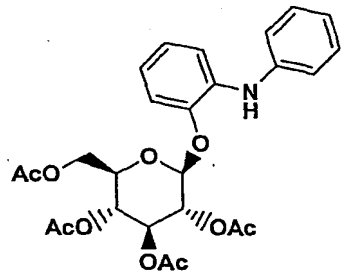
with 250 mL of CH_2Cl_2 and filtered through celite. After washing the celite with additional CH_2Cl_2, the combined rganic fraction was concentrated to yield a yellow residue. Triteration (4X) with MeOH dissolved most impurities to yield 4.15 of the desired title 2-nitrophenyl-O-glucoside.

B.



Crude Part A compound (2g), partially dissolved in 35 mL of 2:2:3 THF/DCE/MeOH containing 0.2 g of 10% Pd/C, was stirred for 5 hr under 1 atmosphere H_2 for 16 hr prior to filtration through celite. The filtrate, including the MeOH washes of the celite pad, were concentrated to yield 1.8 of title o-anilino-O-glucoside.

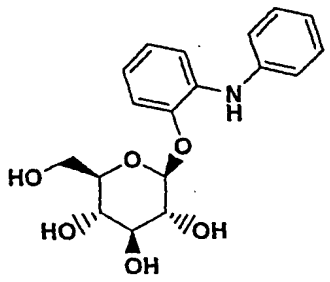
C.



A mixture of Part B compound (100 mg, 0.23 mmol), $Pd(OAc)_2$ (2.5 mg, 0.01 mmol), BINAP (0.8 mg, 0.0014 mmol) and phenyl triflate (51 mg, 0.23 mmol) were stirred for 5 min in PhMe (1 mL) containing 1 drop of Et_3N before adding Cs_2CO_3 (103 mg, 0.32 mmol). Upon heating to 102°, the bright yellow solution became red. After 15 hr HPLC showed a new peak plus residual. An attempt to drive the conversion by addition of the other reaction components

was not successful. The reaction, after cooling to 20°, was diluted with EtOAc and filtered through celite. The filtrate was concentrated and the residue chromatographed on silica gel using 3:7 EtOAc/hexane to elute 10 mg of desired title product.

D.



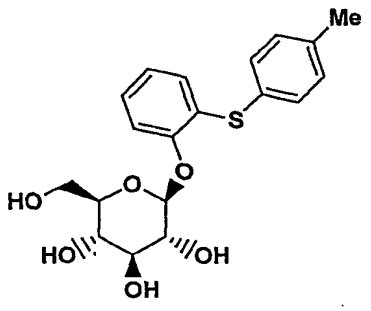
Part C tetra acetate (10 mg, 0.019 mmol) was stirred overnight in 1:2:3 H_2O/THF/MeOH (0.6 mL) containing LiOH (1 mg, 0.023 mmol). The volatiles were removed after neutralization with 1 N HCl. The residue was purified by Prep HPLC on a YMC S5 C18 reverse phase column employing a 10 min. gradient elution (30% to 90% MeOH/H_2O) to obtain 3 mg of final glucoside after lyophilization.

^1H NMR (500 MHz, CD_3OD) δ 3.37-3.52 (m, 4 H), 3.72 (dd, 1 H, J = 5 Hz), 3.89 (dd, 1H, J = 2 Hz), 4.74 (d,1 H, J = 8 Hz), 6.77-7.28 (m, 9 H).

HPLC retention time: 6.2 min, 100 % purity, Zorbax C-18 4.6x75mm, 2.5 mL/min, detection at 220 nm, 8 min gradient 0-100% B hold 3 min at 100% B. Solvent A: 10% MeOH/H_2O + 0.2% H_3PO_4. Solvent B: 90% MeOH/H_2O + 0.2 % H_3PO_4.

Anal Calcd for $C_{18}H_{21}NO_6$ Low Res. MS [M+H] = 348

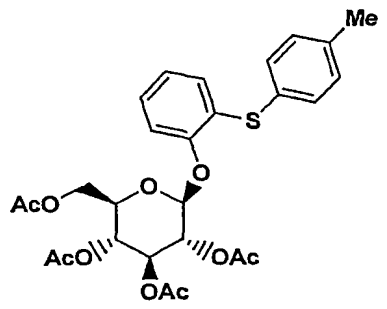
Example 5



A. 2-Hydroxy-4'-diphenyl sulfide

60% NaH/mineral oil (260 mg, 6.5 mmol) was washed with pentane twice prior to being suspended with stirring under Ar in THF (10 mL) at 0° whereupon neat *o*-bromophenol (500 µL, 746 mg, 4.3 mmol) was added. After stirring for 1 hr at 20°, the solution was cooled to -78° and 1.28 M *t*-BuLi/hexane (3.7 mL, 4.7 mmol) was added. After 10 min, 3 mL of a THF solution of *p*-tolyl disulfide (1.06 g, 4.3 mmol) was added. The reaction was stirred for 10 min before warming to 0° at which temperature it was maintained for 1 hr. The reaction was quenched by addition of 2mL of satd aq. NH_4Cl prior to dilution with 150 mL of EtOAc. The EtOAc phase was washed with satd aq. NH_4Cl, dried over $MgSO_4$ and concentrated to yield a yellow oil (910 mg). Chromatography on silica gel using 5:1 hexane/EtOAc yielded 2-hydroxy-4'-diphenyl sulfide (555 mg) as a clear oil.

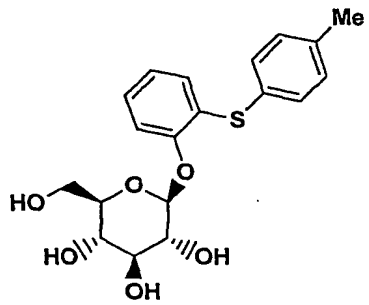
B.



A solution of Part A compound (300mg, 1.39 mmol), 2,6-di-*t*-butyl-4-methylpyridine (387 mg, 1.88 mmol),

2,3,4,6-tetra-O-acetyl- α-D-glucopyranosyl bromide (661 mg, 1.61 mmol) in 9 mL CH_2Cl_2 was stirred until homogeneous prior to cooling to 0°). After addition of AgOTf (456 mg, 1.88 mmol) to the cold solution, the reaction was stirred 2.5 hr prior to addition of additional 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide (274 mg, 0.66 mmol) and AgOTf (157 mg, 0.61 mmol). After 2 hr, the suspension was directly loaded on a silica gel column which was eluted initially with 1:2 EtOAc/hexane. The minor undesired α-anomer (99 mg) eluted first followed by the desired title tetra-acetoxy-β-O-glucoside (660 mg).

C.



Part B tetra-acetate (525 mg, 0.96 mmol) was stirred 6 hr in 1:2:3 H_2O/THF/MeOH (9.6 mL) containing LiOH (40 mg, 1 mmol). The volatiles were removed after neutralization with 1 N HCl. 20% of residue was purified by Prep HPLC on a YMC S5 C18 reverse phase column employing a 10 min. gradient elution (50% to 90% MeOH/H_2O) to obtain 24 mg of final glucoside after lyophilization.

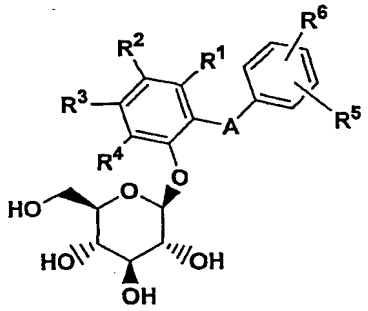
^{1}H NMR (400 MHz, CD_3OD) δ 7.29 (m, 2H), 7.18 (m, 4H), 6.88 (m, 2H), 4.98 (d, 1H, J=7.0 Hz), 3.88 (m, 1H), 3.70 (dd, 1H, J=4.8, 11.9), 3.43 (m, 4H), 2.34 (s, 3H).

HPLC: 6.85 min. retention time; HI=100%; YMC S3 column ODS 4.6x50 mm; 2.5 mL/min, detection at 220 nm, 0-100%B over 8 min, hold for 5 min. Solvent A: 10% MeOH/H_2O+0.2% H_3PO_4. Solvent B: 90% MeOH/H2O+0.2% H3PO4.

Anal Calcd for $C_{19}H_{22}O_6S$ LC-MS: [M+H] 379, [M+Na] 401, [2M+Na] 779.

Examples 6 to 99

In a manner analogous to that of Examples 1 to 5, the compounds of the invention in the following table were prepared.

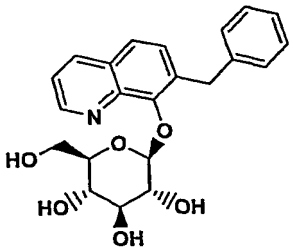


*(R^6= H unless otherwise indicated)

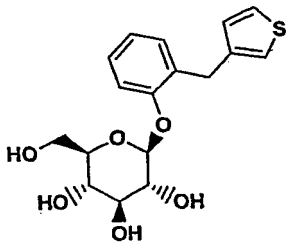
Ex.#	A	R^1	R^2	R^3	R^4	R^5 *	MS or LC/MS (M + H)+
6	CH_2	H	H	H	H	H	347
7	CH_2	H	H	H	H	2-HO	363
8	CH_2	H	H	H	H	4-MeO	377
9	CH_2	H	H	H	H	4-tBu	403
10	CH_2	H	H	H	H	4-MeS	393
11	CH_2	H	H	H	H	4-Ph	423
12	CH_2	H	H	H	H	4-BnO	453
13	CH_2	H	H	H	H	4-*i*Pr	389
14	CH_2	H	H	H	H	4-Cl	381
15	CH_2	H	H	H	H	4-$MeSO_2$	425
16	CH_2	H	H	H	H	4-CF_3	415
17	CH_2	H	H	H	H	4-CF_3O	431
18	CH_2	H	H	H	H	4-OCH_2CO_2H	426
19	CH_2	H	H	H	H	4-OCH_2CO_2Me	435
20	CH_2	H	H	H	H	4-OCH_2CONEt_2	476
21	CH_2	H	H	H	H	4-$OCH_2CH_2NMe_2$	434

22	CH_2	H	H	H	H	4-styrenyl	449
23	CH_2	H	H	H	H	3-Me	361
24	CH_2	H	H	H	H	3-MeO	377
25	CH_2	H	H	H	H	2-MeO	377
26	CH_2	H	H	H	H	2-Et	375
27	CH_2	H	H	H	H	2,4-Me_2	375
28	CH_2	H	H	H	H	3-Cl,4-Me	394
29	CH_2	H	H	H	H	3,4-OCH_2O	391
30	CH_2	Cl	H	H	H	H	381
31	CH_2	Me	H	H	H	H	361
32	CH_2	H	Me	H	H	H	361
33	CH_2	H	F	H	H	H	365
34	CH_2	H	Cl	H	H	H	381
35	CH_2	H	(p-MeBn)	H	H	H	465
36	CH_2	H	Cl	H	H	2-HO,5-Cl	431
37	CH_2	H	Cl	H	Br	H	459
38	CH_2	H	Br	H	Br	H	503
39	CH_2	H	(1,1,3,3-Me_4-Bu)	H	H	2,4-Cl_2	527
40	CH_2	H	H	MeO	H	H	377
41	CH_2	H	H	MeO	H	4-Me	391
42	CH_2	H	H	PrO	H	H	405
43	CH_2	H	H	Me	H	H	361
44	CH_2	H	H	Cl	H	H	381
45	CH_2	H	H	H	Cl	H	381
46	CH_2	H	H	H	Me	4-MeS	407
47	CH_2	H	H	H	Me	4-HO	377
48	CH_2	H	H	H	Me	4-Me	375
49	CH_2	H	H	H	Me	4-$MeSO_2$	439
50	Bond	H	H	H	H	H	333
51	$(CH_2)_2$	H	H	H	H	H	361
52	$(CH_2)_3$	H	H	H	H	H	375
53	OCH_2	H	H	H	H	H	363
54	OCH_2CH_2	H	H	H	H	4-MeO	407

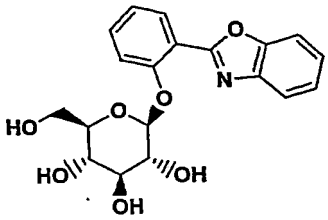
55	NH	H	H	H	H	4-Me	361
56	$NHCH_2$	H	H	H	H	H	362
57	$NHCH_2$	H	H	H	H	4-Me	376
58	$NHCH_2$	H	H	H	H	2,3-Benzo	412
59	$NHCH_2$	H	H	H	H	4-MeO	392
60	$NHCH_2$	H	H	H	H	4-CF_3	430
61	$NHCH_2$	H	H	H	H	3-Me	376
62	$NHCH_2$	H	H	H	H	4- Me_2N	405
63	$NHCH_2$	H	H	H	H	4-MeS	408
64	$NHCH_2$	H	H	H	H	2-Me	376
65	$NHCH_2$	H	H	H	H	2,3-OCH_2O	406
66	$NHCH_2CH_2$	H	H	H	H	H	376



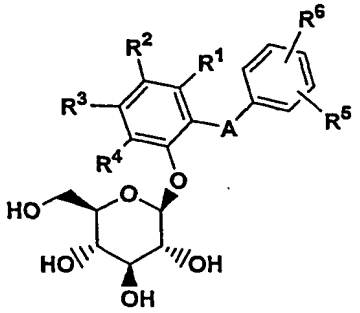
Example 67
M+H 398



Example 68
M+H 353

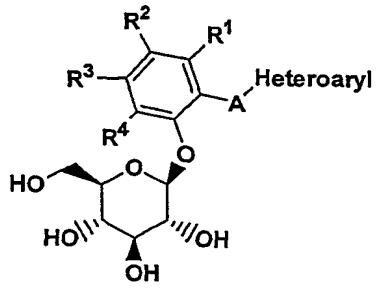


Example 69
M+H 374



*(R^6 = H unless otherwise indicated)

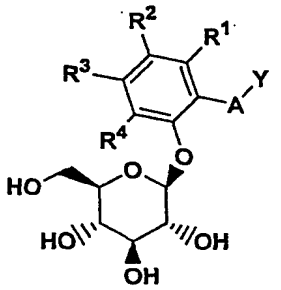
Ex. #	A	R^1	R^2	R^3	R^4	R^5	MS or LC/MS $(M+H)^+$
70	CH_2	Me	H	H	H	4-Me	392(M+NH4)
71	CH_2	Me	H	H	H	4-Et	387 (M-H)
72	CH_2	Me	H	H	H	4-Cl	
73	CH_2	Me	H	H	H	4-MeS	
74	CH_2	Me	H	H	H	4-MeO	
75	CH_2	Me	H	H	H	4-HO	
76	CH_2	Me	H	H	H	4-$MeSO_2$	
77	CH_2	Me	H	H	H	4-CF_3O	502 (M-H+$MeCO2^-$)
78	CH_2	Me	H	H	H	4-CF_3	
79	CH_2	Me	H	H	H	4-Ac	
80	CH_2	Me	H	H	H	4-$HOCH_2$	
81	CH_2	Me	H	H	H	4-CHF_2O	
82	CH_2	H	H	H	Me	4-Et	
83	CH_2	H	H	H	Me	4-CHF_2O	
84	CH_2	H	H	H	Me	H	378 (M+NH4)
85	CH_2	H	H	H	Me	4-Cl	
86	CH_2	H	H	H	Me	4-AC	
87	CH_2	H	H	H	Me	4-$HOCH_2$	
88	CH_2	H	H	H	Me	4-CF_3O	
89	CH_2	H	H	H	Me	4-CH_3O	408 (M+NH4)
90	CH_2	H	H	H	H	4-Ac	
91	CH_2	H	H	H	H	4-$HOCH_2$	
92	CH_2	H	H	H	H	4-CHF_2O	



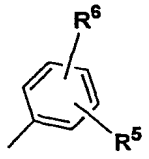
Ex #	A	R^1	R^2	R^3	R^4	Heteroaryl
93	CH_2	H	H	H	H	2-Pyridine
94	CH_2	H	H	H	H	3-Pyridine
95	CH_2	H	H	H	H	2-Oxazole
96	CH_2	H	H	H	H	2-Thiazole
97	CH_2	H	H	H	H	2-Benzthiazole
98	CH_2	H	H	H	H	3-Quinoline
99	CH_2	Me	H	H	H	2-Oxazole
100	CH_2	H	H	H	Me	2-Thiazol
101	CH_2	H	H	H	Me	2-Oxazole

What is claimed:

1. A compound having the structure



wherein

when Y is  or heteroaryl;

R^1, R^2, R^3, and R^4 are the same or different and are independently selected from hydrogen, OH, OR^7, lower alkyl, or halogen, or two of R^1, R^2, R^3, and R^4 together with the carbons to which they are attached can form an annelated five, six or seven membered carbocycle or heterocycle which may contain 1 to 4 heteroatoms in the ring which are N, O, S, SO, and/or SO_2;

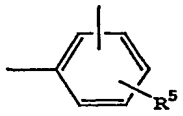
R^5 and R^6 are the same or different and are independently selected from hydrogen, OH, OR^{7a}, -OAryl, $-OCH_2Aryl$, lower alkyl, cycloalkyl, Aryl, arylalkyl, CF_3, arylalkenyl, $-OCHF_2$, $-OCF_3$, halogen, -CN, $-CO_2R^{7b}$, $-CO_2H$, COR^{8f}, $CHOHR^{8g}$, $CH(OR^{7h})R^{8h}$, $-CONR^8R^{8a}$, $-NHCOR^{7c}$, $-NHSO_2R^{7d}$, $-NHSO_2Aryl$, $-SR^{7e}$, $-SOR^{7f}$, $-SO_2R^{7g}$, $-SO_2Aryl$, $-OCH_2CO_2R^{7i}$, $-OCH_2CO_2H$, $-OCH_2CONR^{8b}R^{8c}$, $-OCH_2CH_2NR^{8d}R^{8e}$, or a five, six or seven membered heterocycle which may contain 1 to 4 heteroatoms in the ring which are N, O, S, SO, and/or SO_2, or R^5 and R^6 together with the carbons to which they are attached form an annelated five, six or seven membered carbocycle or heterocycle which may contain 1 to 4 heteroatoms in the ring which are N, O, S, SO, and/or SO_2;

R^7, R^{7a}, R^{7b}, R^{7c}, R^{7d}, R^{7e}, R^{7f}, R^{7g}, R^{7h} and R^{7i} are independently lower alkyl;

R^8, R^{8a}, R^{8b}, R^{8c}, R^{8d}, R^{8e}, R^{8f}, R^{8g} and R^{8h} are the same or different and are independently selected from hydrogen, alkyl, aryl, arylalkyl, cycloalkyl, or together with the nitrogen to which they are attached form an annelated five, six or seven membered heterocycle which may contain 1 to 4 heteroatoms in the ring which are N, O, S, SO, and/or SO_2;

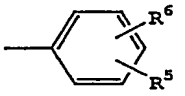
A is $O(CH_2)_m$, S, $NH(CH_2)_m$, or $(CH_2)_n$ where n is 0-3 and m is 0-2, and a pharmaceutically acceptable salt thereof, all stereoisomers thereof, and all prodrug esters thereof,

with the following provisos that where A is CH_2 and Y is R^6



and

1) when R^1 is OH and R^3 is alkyl, at least one of R^1, R^4, R^5 and R^6 is not hydrogen;
2) when R^2 and R^3 are OH, at least one of R^1, R^4, R^5 and R^6 is not hydrogen;
3) when R^2 is methyl, R^5 is OH, and R^6 is alkyl, at least one of R^1, R^3, and R^4 is not hydrogen; and
4) when R^2 is chlorine, at least one of R^1, R^3, R^4, R^5 and R^6 is not hydrogen.

2. The compound as defined in Claim 1 wherein Y is  .

3. The compound as defined in Claim 1 wherein Y is heteroaryl.

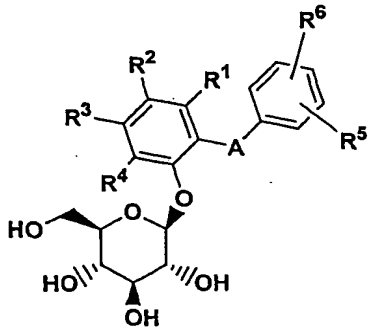
4. The compound as defined in Claim 1 wherein A is $O(CH_2)_m$.

5. The compound as defined in Claim 1 wherein A is S.

6. The compound as defined in Claim 1 wherein A is $NH(CH_2)_m$.

7. The compound as defined in Claim 1 wherein A is $(CH_2)_n$.

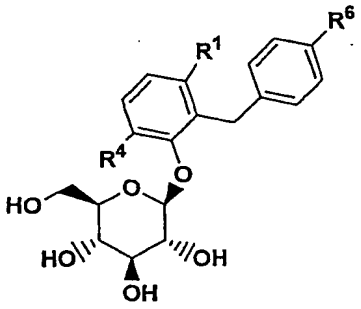
8. The compound as defined in Claim 1 having the structure



wherein A is CH_2 or O or S.

9. The compound as defined in Claim 8 wherein A is CH_2; R^1 is H, halogen, or alkyl, and R^2, R^3 and R^5 are each hydrogen.

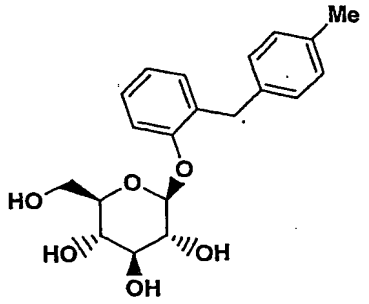
10. The compound as defined in Claim 1 having the structure



where R^1 is hydrogen, halogen, or alkyl or R^1 and R^4 are independently H or alkyl;

R^6 is hydrogen, alkyl, $R^{7a}O$, CHF_2O, CF_3O or $R^{7e}S$.

11. The compound as defined in Claim 1 having the structure



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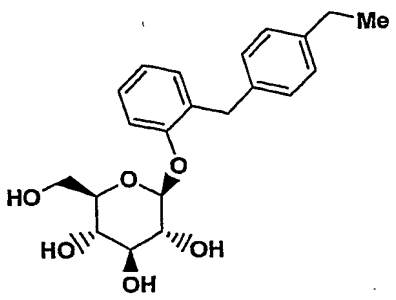

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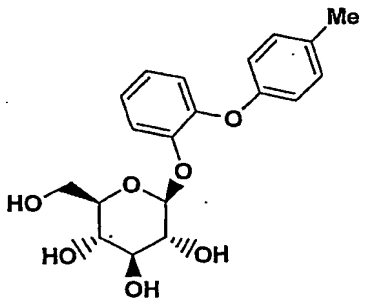

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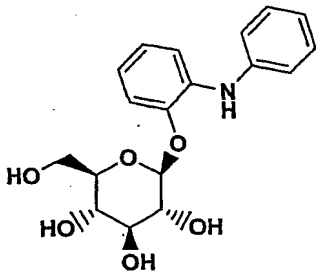

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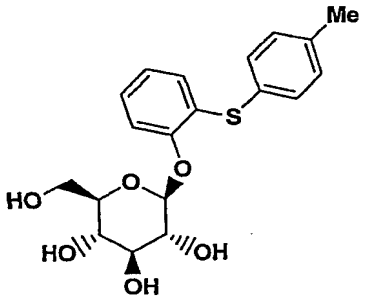

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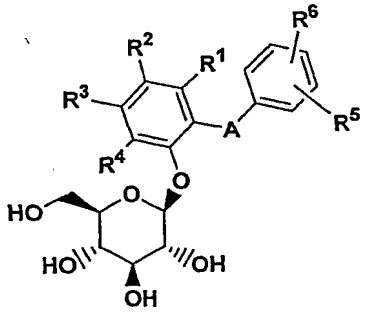
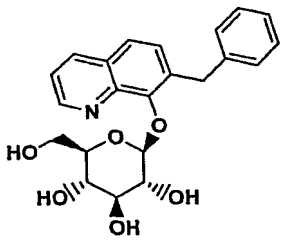


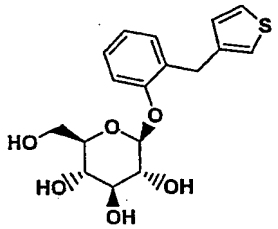
*R^6 = H unless otherwise indicated

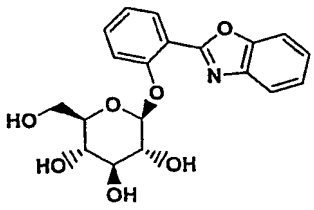
A	R^1	R^2	R^3	R^4	R^5
CH_2	H	H	H	H	H
CH_2	H	H	H	H	2-HO
CH_2	H	H	H	H	4-MeO

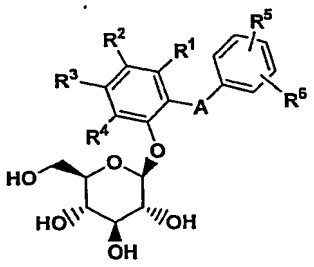
CH_2	H	H	H	H	4-tBu
CH_2	H	H	H	H	4-MeS
CH_2	H	H	H	H	4-Ph
CH_2	H	H	H	H	4-BnO
CH_2	H	H	H	H	4-*i*Pr
CH_2	H	H	H	H	4-Cl
CH_2	H	H	H	H	4-$MeSO_2$
CH_2	H	H	H	H	4-CF_3
CH_2	H	H	H	H	4-CF_3O
CH_2	H	H	H	H	4-OCH_2CO_2H
CH_2	H	H	H	H	4-OCH_2CO_2Me
CH_2	H	H	H	H	4-OCH_2CONEt_2
CH_2	H	H	H	H	4-$OCH_2CH_2NMe_2$
CH_2	H	H	H	H	4-styrenyl
CH_2	H	H	H	H	3-Me
CH_2	H	H	H	H	3-MeO
CH_2	H	H	H	H	2-MeO
CH_2	H	H	H	H	2-Et
CH_2	H	H	H	H	2,4-Me_2
CH_2	H	H	H	H	3-Cl,4-Me
CH_2	H	H	H	H	3,4-OCH_2O
CH_2	Cl	H	H	H	H
CH_2	Me	H	H	H	H
CH_2	H	Me	H	H	H
CH_2	H	F	H	H	H
CH_2	H	Cl	H	H	H
CH_2	H	(*p*-MeBn)	H	H	H
CH_2	H	Cl	H	H	2-HO,5-Cl
CH_2	H	Cl	H	Br	H
CH_2	H	Br	H	Br	H
CH_2	H	(1,1,3,3-Me_4-Bu)	H	H	2,4-Cl_2
CH_2	H	H	MeO	H	H
CH_2	H	H	MeO	H	4-Me
CH_2	H	H	PrO	H	H
CH_2	H	H	Me	H	H

CH_2	H	H	Cl	H	H
CH_2	H	H	H	Cl	H
CH_2	H	H	H	Me	4-MeS
CH_2	H	H	H	Me	4-HO
CH_2	H	H	H	Me	4-Me
CH_2	H	H	H	Me	4-$MeSO_2$
Bond	H	H	H	H	H
$(CH_2)_2$	H	H	H	H	H
$(CH_2)_3$	H	H	H	H	H
OCH_2	H	H	H	H	H
OCH_2CH_2	H	H	H	H	4-MeO
NH	H	H	H	H	4-Me
$NHCH_2$	H	H	H	H	H
$NHCH_2$	H	H	H	H	4-Me
$NHCH_2$	H	H	H	H	2,3-Benzo
$NHCH_2$	H	H	H	H	4-MeO
$NHCH_2$	H	H	H	H	4-CF_3
$NHCH_2$	H	H	H	H	3-Me
$NHCH_2$	H	H	H	H	4- Me_2N
$NHCH_2$	H	H	H	H	4-MeS
$NHCH_2$	H	H	H	H	2-Me
$NHCH_2$	H	H	H	H	2,3-OCH_2O
$NHCH_2CH_2$	H	H	H	H	H



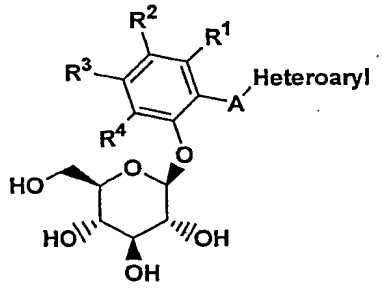






*R^6 = H unless otherwise indicated

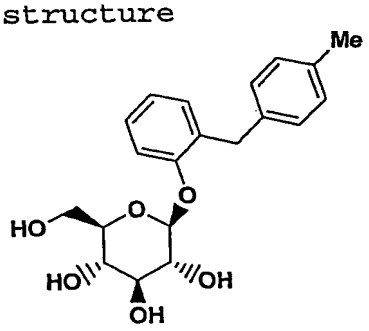
A	R^1	R^2	R^3	R^4	R^5
CH_2	Me	H	H	H	4-Me
CH_2	Me	H	H	H	4-Et
CH_2	Me	H	H	H	4-Cl
CH_2	Me	H	H	H	4-MeS
CH_2	Me	H	H	H	4-MeO
CH_2	Me	H	H	H	4-HO
CH_2	Me	H	H	H	4-$MeSO_2$
CH_2	Me	H	H	H	4-CF_3O
CH_2	Me	H	H	H	4-CF_3
CH_2	Me	H	H	H	4-Ac
CH_2	Me	H	H	H	4-$HOCH_2$
CH_2	Me	H	H	H	4-CHF_2O
CH_2	H	H	H	Me	4-Et
CH_2	H	H	H	Me	4-CHF_2O
CH_2	H	H	H	Me	H
CH_2	H	H	H	Me	4-Cl
CH_2	H	H	H	Me	4-AC
CH_2	H	H	H	Me	4-$HOCH_2$
CH_2	H	H	H	Me	4-CF_3O
CH_2	H	H	H	H	4-Ac
CH_2	H	H	H	H	4-$HOCH_2$
CH_2	H	H	H	H	4-CHF_3O



A	R^1	R^2	R^3	R^4	
CH_2	H	H	H	H	2-Pyridine
CH_2	H	H	H	H	3-Pyridine
CH_2	H	H	H	H	2-Oxazole

CH_2	H	H	H	H	2-Thiazole
CH_2	H	H	H	H	2-Benzthiazole
CH_2	H	H	H	H	3-Quinoline
CH_2	H	Me	H	H	2-Oxazole
CH_2	H	H	H	Me	2-Thiazol
CH_2	H	H	H	Me	2-Oxazole

12. The compound as defined in Claim 1 having the structure



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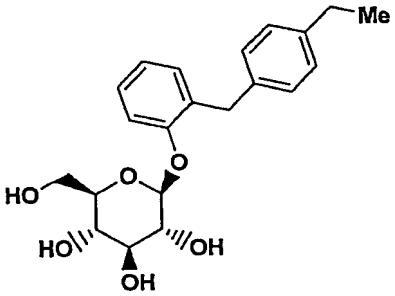

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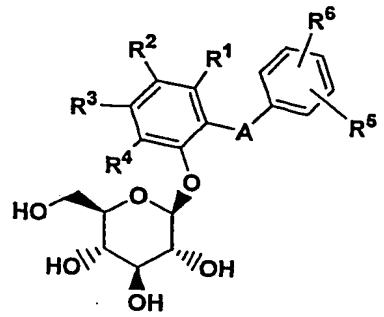


*R^6 = H unless otherwise indicated

A	R^1	R^2	R^3	R^4	R^5
CH_2	H	H	H	H	4-MeO
CH_2	H	H	H	H	4-tBu
CH_2	H	H	H	H	4-MeS
CH_2	H	H	H	H	4-iPr
CH_2	H	H	H	H	4-Cl
CH_2	H	H	H	H	4-CF_3
CH_2	H	H	H	H	4-CF_3O
CH_2	Me	H	H	H	H
CH_2	H	H	H	Me	4-MeS
CH_2	H	H	H	Me	4-Me
CH_2	Cl	H	H	H	H

13. A pharmaceutical composition comprising a compound as defined in Claim 1 and a pharmaceutically acceptable carrier therefor.

14. A pharmaceutical combination comprising an SGLT2 inhibitor compound as defined in Claim 1 and an antidiabetic agent other than an SGLT2 inhibitor, an anti-obesity agent, and/or a lipid-lowering agent.

15. The pharmaceutical combination as defined in Claim 14 comprising said SGLT2 inhibitor compound and an antidiabetic agent.

16. The combination as defined in Claim 15 wherein the antidiabetic agent is 1, 2, 3 or more of a biguanide, a sulfonyl urea, a glucosidase inhibitor, a PPAR γ

agonist, a PPAR α/γ dual agonist, an aP2 inhibitor, a DP4 inhibitor, an insulin sensitizer, a glucagon-like peptide-1 (GLP-1), insulin and/or a meglitinide.

17. The combination as defined in Claim 16 wherein the antidiabetic agent is 1, 2, 3 or more of metformin, glyburide, glimepiride, glipyride, glipizide, chlorpropamide, gliclazide, acarbose, miglitol, pioglitazone, troglitazone, rosiglitazone, insulin, Gl-262570, isaglitazone, JTT-501, NN-2344, L895645, YM-440, R-119702, AJ9677, repaglinide, nateglinide, KAD1129, AR-HO39242, GW-409544, KRP297, AC2993, LY315902, and/or NVP-DPP-728A.

18. The combination as defined in Claim 15 wherein the compound is present in a weight ratio to the antidiabetic agent within the range from about 0.01 to about 300:1.

19. The combination as defined in Claim 14 wherein the anti-obesity agent is a beta 3 adrenergic agonist, a lipase inhibitor, a serotonin (and dopamine) reuptake inhibitor, a thyroid receptor beta compound, and/or an anorectic agent.

20. The combination as defined in Claim 19 wherein the anti-obesity agent is orlistat, ATL-962, AJ9677, L750355, CP331648, sibutramine, topiramate, axokine, dexamphetamine, phentermine, phenylpropanolamine, and/or mazindol.

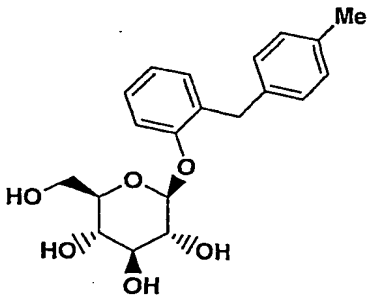
21. The combination as defined in Claim 14 wherein the lipid lowering agent is an MTP inhibitor, an HMG CoA reductase inhibitor, a squalene synthetase inhibitor, a fibric acid derivative, an upregulator of LDL receptor activity, a lipoxygenase inhibitor, or an ACAT inhibitor.

22. The combination as defined in Claim 21 wherein the lipid lowering agent is pravastatin, lovastatin, simvastatin, atorvastatin, cerivastatin, fluvastatin, nisvastatin, visastatin, fenofibrate, gemfibrozil, clofibrate, avasimibe, TS-962, MD-700, and/or LY295427.

23. The combination as defined in Claim 21 wherein the aP2 inhibitor is present in a weight ratio to the lipid-lowering agent within the range from about 0.01 to about 100:1.

24. A method for treating diabetes, diabetic retinopathy, diabetic neuropathy, diabetic nephropathy, wound healing, insulin resistance, hyperglycemia, hyperinsulinemia, Syndrome X, diabetic complications, or elevated blood levels of free fatty acids or glycerol, hyperlipidemia, obesity, hypertriglyceridemia, atherosclerosis, hypertension, or for increasing high density lipoprotein levels, which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of a compound as defined in Claim 1.

25. The method as defined in Claim 24 where the compound administered has the structure



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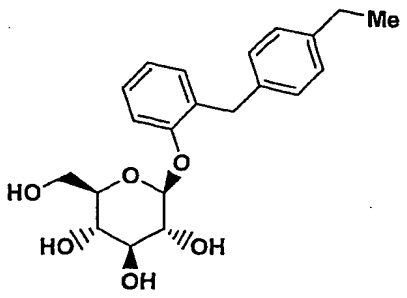

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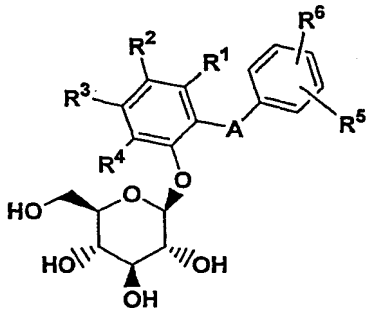

*R^6 = H unless otherwise indicated

A	R^1	R^2	R^3	R^4	R^5
CH_2	H	H	H	H	4-MeO
CH_2	H	H	H	H	4-tBu
CH_2	H	H	H	H	4-MeS
CH_2	H	H	H	H	4-iPr
CH_2	H	H	H	H	4-Cl
CH_2	H	H	H	H	4-CF_3
CH_2	H	H	H	H	4-CF_3O
CH_2	Me	H	H	H	H
CH_2	H	H	H	Me	4-MeS
CH_2	H	H	H	Me	4-Me

26. A method for treating type II diabetes which comprises administering to a mammalian species in need of treatment a therapeutically effective amount of a compound as defined in Claim 1 alone or in combination with one, two or more other antidiabetic agent(s), and/or one, two or more hypolipidemic agent(s).

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/10092

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07H15/203 A61K31/7034 A61P7/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07H A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	T.H. BEMBRY, G. POWELL: "The synthesis of phenolic glycosides" J. AM. CHEM. SOC., vol. 64, 1942, pages 2419-2420, XP002174938 page 2420, right-hand column, line 8 - line 13	1,2,7,11
X	WO 99 31036 A (CIBA GEIGY AG ;MAO JIANWEN (DE); HUEGLIN DIETMAR (DE); MAIER THOMA) 24 June 1999 (1999-06-24) example 1	1,2,4,8
A	EP 0 598 359 A (TANABE SEIYAKU CO) 25 May 1994 (1994-05-25) cited in the application the whole document	1,14

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 August 2001	25/09/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	de Nooy, A

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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